The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference

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Workgroup 1 – Pathophysiology

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Dr. Barry Wilson, PhD, Chair
Professor, Department of Animal Science and
Department of Environmental Toxicology
University of California, Davis
Davis, California

Okay, we're going to get started now. As we're starting at 20 after 4:00, instead of at 4:00, we will run an equal amount out, so we'll be done at 5:40, 5:50. Okay, my name is Barry Wilson. I'm the chair of session, and I want to welcome you to our work group. Now, this workgroup is different from what any of us are familiar with because most of us when we're in a workgroup we figure it's in a room the doors are closed and here we are the gold fish and the rest of you are the bowl. And we're going to try to make this a two-way street in the next few days as we work out this session. So first let me introduce quickly and then we'll move on. Dr. Norris who's not on my list because I made a mistake, didn't type it all in last night. Dr. Somani, Dr. Bell, Sorg, maybe I'll leave off the doctors; they all are. Soreq, Spencer, Peckerman, Korenyi-Both, I got it right, Miller, Ashley, and Abou-Donia.

Now if you multiply 13 of us, maybe now it's 12 because I don't know where Dr. Jamal is, it comes out 96 minutes, we have only 120 for what we're doing. So we need to move, I need to ask our panel, our distinguished panel, to keep to our business as much as we can so we can allow time for the number of people I've seen all day, that stand at those microphones because this has to be a two-way street for it to function well.

The charge of this session is to develop recommendations for future research. To address the concerns of Gulf War veterans' health. Our focus here is on chemical exposures and on illnesses among Gulf War veterans, pathophysiology, etiology, and mechanisms of action. The suggestions that were given to us are synergistic effects of chemicals, sub-clinical effects of chemicals, susceptibility, biomarkers of susceptibility and of exposure and study methods for determining mechanisms and etiology. It's a full plate.

Our purpose is, what I as chair am proposing, and what this marvelous workgroup could dispose, I hope, that is to look towards the future with our feet firmly based in past experiences and in past research. This is a very distinguished group of scientists. Our role is to identify knowledge gaps, propose ways to fill them, justify that in terms of the research for the veteran, the veteran of today and the veteran of tomorrow. The process I propose here is for us to list the important unfulfilled directions of research, whether or not they're the favorite one going on in my laboratory. To reduce that list, regroup it, prioritize it and give our report by next Tuesday.

Let me lay on the table some simple criteria for all of us. The best science must drive this. Not if wishing could make it so, but what do we have in data, on the table. Second, testable hypotheses. Relevance to veterans, addressing data gaps. What do we need to learn more of? Avoid undue duplication of existing projects. Understanding though that, because somebody has found something once doesn't mean their colleague might not find it again. We've all been there, done that.

There's a lot of epidemiology that will be in the other workgroups. Our focus is not necessarily epidemiology. Studies of chemical mixtures, effects on experimental animals, if it's ongoing work, the beginning of genetic sensitivity studies. Several around this panel have done that. Ways to screen for sensitive physiologies, roles of animals, cellular models, their validations, paradigms of studying multiple stressors and chemical mixtures, testing the chemical prophylactic combinations that may pose less risk to those taking them -- establishing at the bottom line, how things happen and how they work for the veterans, as I said, of the past, here today, and of the future.

Let me pose for you a paradigm for you to think about. Single level research is only descriptive, it does not establish a mechanism. If you think of the hierarchy of life from molecule to cell to organ to animal to population, single level work never gets beyond description. To get to a mechanism you need to go one level down. The significance, one level up. Now this probably, sophistry if you're a philosopher, works pretty well for biologists. I'm not going to take the time to give out the examples of it, but it's something to judge as we judge our research. If it's single level we may not be doing our job at this workgroup.

So here's a few examples: on the population level you got screens for sensitive populations. Individual levels, you test hypotheses, separating sensitizing from eliciting physiological effects,

the delay. At the organ level you get the physiological basis for multiple chemical pathologies. At the cell level you can find out the mechanisms by which the organs have been compromised and you can also provide some alternatives to animal research, to screen for drug and aging effects. At the molecular level you get the genetic makeup and physiological outcomes.

So in closing, we're not here to present our brilliant research except in so far as to document what we need to be working on and to establish who each of us are. We're not here to replace data with rhetoric. And now I've managed to offend everybody in this room by the first 2 sentences. But we are here to chart a course for Gulf War research for 3 years, for 5 years, and maybe beyond. And I want to thank Drue Barrett, and the committee, that have asked us here, because it's an honor for me to chair this group no matter what blood happens later as we have to hammer out our priorities. We're also here to listen and harken to our colleagues and our veteran partners. That's why we must take our time quickly so there's enough room for all of you in the next couple of days. So we speak together. The recent release of several Gulf War research requests that many of you know about, attest to the liveliness of this research and the perceived need for studies.

And I close simply with this part, all have a right to speak, all of us have an obligation to listen and we all have a need to learn. That's my introduction.

Leslie Simpson, MSc, PhD
Red Blood Cell Research Trust
Dunedin, New Zealand

Mr. Chairman?

Dr. Barry Wilson, Chair

Yes, sir.

Dr. Leslie Simpson

Are we going to proceed to panelize this discussion?

Dr. Barry Wilson, Chair

Yes.

Dr. Leslie Simpson

The point is, I have written a pathogenesis of Gulf War syndrome. If the pattern here follows the

pattern that we've had so far, I'll be on my way home and never get a chance to talk bout it.

Dr. Barry Wilson, Chair

Well our panel, I said, sir, the way we set this up is that if you take 8 minutes for each one of us, there's going to be not much time for things. Now how long do you have for your presentation?

Dr. Leslie Simpson

Well I haven't got a presentation as such, but I can certainly talk about it. You tell me how long and I'll talk about it.

Dr. Barry Wilson, Chair

Then let's see how much time we have after we've conducted our business here. Okay? And if you're not on today, you're on tomorrow. That's a guarantee.

CAPT Peter Mazzella
Director, Office of Military Liaison and Veterans' Affairs
Office of Public Health & Science
Department of Health and Human Services
Washington, DC

What we announced this morning is that there is a sign-up sheet for all those individuals who wish to present their information. We need to have whoever wants to present to sign up at the information sheets so that we can gauge the amount of time that we can allow individuals to speak. It's right across from the registration desk.

Audience Member

I think the gentleman has a point, in all candor, we went through this the night before. And you're correct, these are all very well established individuals with the research, including yourself.

Dr. Barry Wilson, Chair

That's right. Your point sir?

Audience Member

But, the point is, that some of us actually have done what was asked and have proposed something, it won't take more than 3 minutes to read it.

Dr. Barry Wilson, Chair

I am not going to give you time now, sir. We're going to proceed with the arrangement we have and then we will work in the time. Did you sign up out there?

Audience Member

Yes, sir.

Dr. Barry Wilson, Chair

Okay, then you will get on. You sir, have to sign up.

Dr. Claudia Miller
Associate Professor
Department of Family Practice
University of Texas Health Sciences Center
San Antonio, Texas

Mr. Chairman, a couple of us are talking and right now I don't have a lot to present, I mean I might take a minute. And I wonder if we could find out from people, sort of poll them, about how much time they think they could limit their remarks to initially so we yield most of the balance to the people who are here.

CAPT Peter Mazzella

Doctor, could you talk into the microphone, because we're recording.

Dr. Claudia Miller

Certainly.

Dr. Barry Wilson, Chair

The suggestion was for us to quickly poll, and that's quickly because we're burning up time while we're on procedures here, because I said a two-way street, and now you figure I'm someone you can roll over.

Dr. Deborah Norris
Neurotoxicologist
U.S. Environmental Protection Agency

Office of Pollution Prevention and Toxics
Washington, DC

Five minutes.

Dr. Barry Wilson, Chair

Your want 5. Somani?

Dr. Satu Somani
Professor of Pharmacology and Toxicology
Department of Pharmacology
Southern Illinois University School of Medicine
Springfield, Illinois

Seven to eight minutes.

Dr. Barry Wilson, Chair

Seven to eight. Is the facilitator adding these up? I can't add and rub my belly at the same time.

Dr. Iris Bell
Staff Physician
Department of Psychiatry
Tucson Veterans Affairs Medical Center
Tucson, Arizona

It would be the same for me, the maximum.

Dr. Barry Wilson, Chair

Which? The maximum. Okay we've got 2 maximums and 1 five.

Dr. Barbara Sorg
Assistant Professor
Program in Neuroscience
VCAPP Department
Washington State University
Pullman, Washington

Three.

Dr. Barry Wilson, Chair

Three. OK, I'm going to take two more for my stuff.

Dr. Hermona Soreq
Professor of Molecular Biology
Head, Life Sciences Institute
Hebrew University of Jerusalem
Life Sciences Institute
Jerusalem, Israel

Seven.

Dr. Peter Spencer
Professor and Director
Center for Research on Occupational and Environmental Toxicology
Oregon Health Sciences University
Portland, Oregon

Four and a quarter.

Dr. Barry Wilson, Chair

Four and a 1/4 and I will hold him to that.

Arnold Peckerman, PhD
Assistant Professor, Department of Neurosciences
University of Medicine and Dentistry of New Jersey
Director, Psychophysiology Laboratory
Gulf War Research Center
East Orange VA Medical Center
East Orange, New Jersey

Seven to eight.

Dr. Barry Wilson, Chair

Seven to eight.

COL Andras Korenyi-Both
Comprehensive Medical Network

Old Forge, Pennsylvania

Eight minutes, sir.

Dr. Barry Wilson, Chair

Eight.

Dr. Claudia Miller

If Dr. Spencer's going to do 4 1/4, I'll do 4.

Dr. David Ashley
Chief, Air Toxicants Branch
National Center for Environmental Health
Centers for Disease Control and Prevention
Atlanta, Georgia

I just have 30 seconds, 2 minutes, something like that.

Dr. Barry Wilson, Chair

Okay, you get 2.

Dr. Mohamed Abou-Donia
Professor, Department of Pharmacology
Duke University Medical Center
Durham, North Carolina

Three minutes.

Dr. Barry Wilson, Chair

Three minutes. What does that add up to? I think it adds up to enough so that you can see how we're going to get to some questions. We also have to start working out our priorities and produce a list, which I hope we can do in 15 minutes. Well I'm trying. Remember, the charge is to come up with research stuff. It's not a forum, it's a workgroup. There is a forum tonight, you know. What do you have? Sixty, that's an hour. So if we took 15 to try to work it up. So, let's go.

Okay, let me tell you what I do and why I'm here. First of all, I work on cholinesterases in blood,

and I'm setting the standards for the state of California. I've shown the clinical kits for cholinesterases is the most, the one that's used the most is off by 40%. I'm working on finger stick measurements, the test made kit that was bought by the military, I've tested, it doesn't work well at lower temperatures. We need to do some work on that.

I've also have studied neuromuscular diseases quite a bit with Dr. Spencer. We have a Gulf War grant to look at pyridostigmine bromide and sarin, organophosphate induced neuropathy, muscle problems, morphometry, and biochemistry. That's the kind of thing I do. Now, let's start around. Dr. Norris.

Your recommendations by the way, will be taken down and then we'll show them. So we'll see what we have as a list. That's how we can get to this.

Dr. Deborah Norris

Okay. I am with the U.S. Environmental Protection Agency and I'm a neurotoxicologist. I work on developing testing programs and guidelines for neurotoxicity. We're testing for the Office of Pollution Prevention and Toxics.

Given our task of developing research recommendations for future study of pathophysiology, etiology, and mechanism of action to possible chemical exposures and illnesses among Gulf War veterans, I thought it would be of interest to tell you about several related efforts and areas of interest at EPA.

One related EPA project has involved the development of guidance, for the estimation of health risk from exposure to multiple chemicals. Although most environmental health risk assessments are for single chemical exposures, many procedures and models have been published dealing with toxicity and risk of multi-chemical exposures referred to as chemical mixtures. These models and procedures range from purely conceptual approaches to official guidelines for regulatory and research purposes.

In 1986, EPA published *Guidelines for Health Risk Assessment for Chemical Mixtures*. It is my thought that these guidelines, and my knowledge of these guidelines, can help us today in developing testing programs for Gulf War. For EPA concerns, exposure and toxicity data are most likely to be available on highly complex mixtures, generated in large quantities. These mixtures are associated with or suspected of causing adverse health effects. Some of these mixtures include pesticides, diesel exhaust, incinerator or coke oven emissions, and we're also interested in land fills.

However the EPA risk assessment and testing guidelines provide some insights towards development of a research program for Gulf War illness. Next slide please.

EPA has an interactions toxicity data base, and we have a support document for our health risk assessment guidelines for mixtures. This support document was published in 1990. And one of the goals of this document was to publish all the information known on chemical mixtures – the document's not very big. We are 9 years from that point in time and we do have some more, my colleagues here on this panel have produced a great deal more data on mixtures. But we need more.

The EPA mixtures toxicity data base is more up to date than this technical support document and contains a great deal of information on toxicity of chemical mixtures. By definition, mixtures consist of those chemicals regardless of spatial or temporal proximity that contribute to the actual or potential toxic effects.

The 1986 U.S. EPA guidelines considers either sequential or simultaneous exposures from multiple chemicals and by several variable exposure routes. According to these guidelines the preferred method for estimating risk is first based on the actual mixture of concern. If that data is not available, the second priority is to base the risk assessment on testing of a mixture that is known to be toxicologically similar to the mixture of concern. The least preferred method is to base the assessment on data for the individual chemical components of the mixture.

One of the problems in basing your risk assessment on the individual components is that it requires an assumption of additivity of chemical toxicity. And additivity may underestimate the risk that you're actually dealing with.

I'm into 3 minutes? Okay 2 more. I'm into my last slide.

The definitions that EPA uses, future research needs to focus on determining toxicological action of the chemicals to which Gulf War soldiers were exposed and the interaction of these toxicological effects. Chemicals can interact in simple additive ways and I'll try to abbreviate here some examples, Aldrin and Eremite both increase mortality and when administered together the observed mortality is equal to the sum of the mortalities observed for each compound alone. Interactive effects, such as synergism, as a response to a mixture of toxic chemicals that's greater than that suggested by the component toxicities. A pharmacological example of that is cocaine and ethanol.

Antagonism, both 2-4-D butyl and 2-4-5T butyl produce teratogenic effects and fetal mortality when given alone, however the effect seen when both compounds are given together is much less severe than either given alone. Potentiation is a special case of synergism., one that I think we'll be very interested in, in which one substance does not have a toxic effect on a certain organ or system, but when added to another chemical, it does, it makes the latter much more toxic. Acetone and acetylnitrile are examples. Vinylidene chloride promoted the degeneration change in liver enhanced by co-administration of acetone, whereas acetone alone has no effect on the liver.

And inhibition is a special case of antagonism in which one substance does not have a toxic effect on a certain organ but when added to the other it makes it less toxic.

In addition to studies on mixtures such as the recent work of our colleagues on this panel, more research is needed to determine whether these chemicals work by simple additive mechanisms or if their toxicity is enhanced by interactive mechanisms such as synergy and potentiation.

I'll stop. Thank you.

Dr. Barry Wilson, Chair

Thank you. Dr. Somani.

Dr. Satu Somani

We are working on interaction of pyridostigmine, sarin, and physical exercise and neurotoxic effects. The first set of experiments which we carried on, of the one we are presenting, we are currently working on pyridostigmine, sarin, and physical exercise. These experiments are going on. But we have worked just on pyridostigmine and exercise and that is what I'm going to present now. And I think I have given the handout to many, and many of you might have these handouts so you can look at it. What I'm presenting is just a summary of my experiments because of the lack of time. We talked about stress and a lot of things have been talked about stress. Different kinds of stress there, but we are taking physical stress as a parameter. That is the forced exercise, exercise on the treadmill. Can this forced exercise amplify the delayed effects of pyridostigmine in cerebral and peripheral tissues of the mice? That's our hypothesis. Next slide please.

These are the different objectives, to study exactly effects of the physical stress and pyridostigmine in mice and to determine biochemical changes. There is a cholinesterase, creatinine phosphokinase, lipid peroxidation, electrophysiological changes, muscle tension, and histopathological changes in cerebral and peripheral tissues.

What we try to do is to simulate the conditions of the Gulf War. We give the exercise for 4 weeks to the mice, then 2 weeks of the treatment of pyridostigmine, oral treatment of dosages the same as the soldiers were taking in the Gulf War. That is, they took 30 mg tablets, 3 times a day, 90 mg dose. We are giving mice the same thing, 1.2 mg per kilogram dose. So, and the physical exercise is essential for all Army people, and they go with this physical exercise. So, we have simulated that condition. And it's quite possible that the interaction of physical stress and the pyridostigmine and its metabolates can enhance the toxic effects of the pyridostigmine.

Since the Gulf War veterans underwent physical stress and were exposed to pyridostigmine, the

interactive and delayed effects of the pyridostigmine were investigated under conditions which reasonably simulate heavy military duty. Now this presentation is confined to investigation of interaction of delayed effects of pyridostigmine and exercise training on biochemical indices, and the muscle tension. Next slide please.

Now as you will see the different groups over here, one is the control group, then the treatment exercise, and the pyridostigmine, and the pyridostigmine and exercise. The results of these are, next slide.

Now our summary of the results is the butyryl cholinesterase and the acetyl cholinesterase activities significantly decreased in plasma and tricep muscle of mice with respect to, only after sub-chronic treatment with pyridostigmine and training on the treadmill. The interaction with pyridostigmine and physical stress resulted in an increase in the plasma creatinine phosphokinase activity, indicating enhanced neuromuscular damage. And enhanced liver peroxidation in the tricep muscle of mice indicating the toxicity to stress response, that is due to the physical stress. Next slide please.

Now our results on the whole indicate that the physical stress enhances the delayed effects of pyridostigmine, primarily in the peripheral tissues of the mice. Physical exercise, as you know, it generates the free radicals. And the free radicals can cause the stress.

Now I come to the sum of the research talks, and my research talks are really related to the intra-action of the physical stress of treadmill exercise with the agent pyridostigmine or sarin. Next slide please.

Here I need to say that this is a physiological flow. Pharmacokinetic and pharmacodynamic modeling of pyridostigmine in central and peripheral compartments under the influence of physical stress. This modeling can predict the toxicity or can also predict the effects of the pyridostigmine. And I think this modeling is very useful and it has been worked out with many chemical compounds which cannot be determined chemically or biologically at a sub-concentration levels. Next slide please.

As I said that mine is really related to physical exercise. But we don't know if the exercise is a low intensity for a long period of time, or a high intensity exercise for a shorter period of time. Now what is the effect of a very low level of sarin? It's really not known under the influence of exercise, so we need to know what happens to the neurons, what happens to the cholinesterase, how much it is destroyed or how much it is regenerated, in what amount of time. Next slide please.

Again we talk here about the effects of the physical stress, exercise, on pyridostigmine induced central and peripheral toxicity in routings that is again related to carbamylation and the half life of

the half time of the generation of the enzyme. Because the Gulf War people took the pyridostigmine and they are seeing the effect after a long time. So how much time it really takes for the generation of the enzyme, or pyridostigmine, is it doing something more to the central system because of the physical stress? Next slide please.

The effects of different modes of physical stress, different types of exercise have different effects. Free wheel exercise, you are freely exercising or forced exercise of the same exercise. We need to see what these different exercises will have the effects. Next slide please.

What, I think I need to stop here, because the chairman has said cutoff.

Dr. Barry Wilson, Chair

No, you don't have to cutoff so fast. Make a closing statement.

Dr. Satu Somani

What I wanted to say is physical exercise, as it generates the free radical, and this free radicals are very damaging. But also the physical exercise generates or enhances the antioxidant enzymes. That is how the normal people, when they exercise, that's the biochemical benefit. But in a diseased condition or in the presence of the other chemicals, are there more generation of the free radicals which are damaging more rather than giving a benefit, due to the physical exercise? Nobody has known. But we have done considerable work under this one and I felt there may be the involvement of the free radical which may be damaging the central system. This is all I want to say.

Dr. Barry Wilson, Chair

Before we go on I want to remind the speakers that our purpose is to come up with recommendations for future research. If your recommendations are very specific we'll have to enlarge them as we present them, so for example, studies of toxicodynamics. Also would you please tell me how much time you want when you start talking? I didn't write those down. So now having laid all that burden on Dr. Bell.

Dr. Iris Bell

I said the maximum, so what is that about 7 or 8 minutes?

Dr. Barry Wilson, Chair

Yeah, that's about 7 minutes, I'm shaving it a little.

Dr. Iris Bell

Okay, well let me talk even faster. I'm not going to go through the details of this. What my take-home message is that I feel that sensitization is a very promising mechanism for at least a substantial subset of Gulf War syndrome cases and since we have a lot of evidence in civilians that seems to point in that direction, I think we should consider exploring it in a variety of models, both human and animal. And I'm not going to go through some of the specifics other than to point out both in our own work and in other individuals' work, there is convergent evidence if you're looking with a hypothesis-driven approach rather than simply fishing, to find support for the involvement of the limbic system in a variety of things, both self-reported material, medical history information and EEG sensitization.

This is an example in 900 college students that the higher the level of chemical intolerance, the higher the symptomatology of limbic dysfunction as measured by a self-report scale that has been tested in temporal lobe epileptics and is believed to be a reflection of their dysfunction.

This is just a slide to demonstrate that after chemical exposure in the chemically intolerant without life style change we saw sensitization of delta activity in the brain. Which is a slow wave activity. We did not see it in the people with life style change and I want to make this point, from a methodologic perspective we're repeatedly in this particular small study finding differences between people who have done something about their problem by avoiding it and the people who haven't. And I suspect this model will not turn out to have the same results depending on who studies which subset.

I'm not going to belabor the sensitization. The evidence here summarizes the individual difference factors which we found in the animal literature suggesting more sensitizable animals. Because I think one area in sensitization that needs to be looked at is who's vulnerable within the veteran population and within the active military. Women report this more men. Carbohydrate craving, I talked about food addiction or cravings. We repeatedly find measures of that elevated. We find increased family histories of drug or alcohol problems, which is a genetic vulnerability. And associated with this genetic vulnerability we're finding this increased alpha activity in the chemically intolerant and this is also been found in the male and female offspring of alcoholics. I'm not proposing that this is a psychosocial thing, I'm proposing that it's a genetic thing. And I will for interest of time keep moving.

Further information, we showed you a slide like this earlier, those with an identifiable chemical initiator actually had the highest rate of paternal alcoholism. So again in terms of clues for genetic factors that we might be looking towards, this may be an area to explore in terms of combining literatures. Another important point is that there is an old literature on alcoholism that the female offspring of type 2 male alcoholics have increased rates of somatization disorder, but not alcoholism. This sounds remarkably similar to what we're talking about if you're labeling these

individuals with Persian Gulf syndrome or MCS as somatizers.

I already made my point about that. We have some other physiologic data related. Environmental factors will increase sensitizability, such as pre-natal stress on the mother, and isolated verses enriched early environment, and there are some studies parallel to this in post-traumatic stress disorder, for which sensitization is also a model as well as being a model for recurrent affective disturbances. And any stress that will reduce pre-frontal cortex dopamine could have an influence like that. And by stress I do not mean just psychosocial stress I am also meaning heat stress which was a very prominent factor in the Gulf, as well as the physical stress.

So the possible sources could range anywhere from earlier stress in the individual's life, drugs of abuse, prior peak acute chemical exposures, repeated chemical exposures at lower levels, interactions certainly of multiple factors from multiple classes which could interact in such a way as to increase the sensitization potential in that individual, and potentially even certain foods that the person might find particularly important. We, as I indicated earlier we have data in several different studies now to show that chemically intolerant people report higher levels of early life stress and so I know that the military takes some look at that, but they obviously don't want to screen people out just because of early life stress.

This was a recent study in our laboratory that's now in press in *Toxicology and Industrial Health*, Dr. Fernandez is the first author. And she found notably that propylene glycol and peppermint tended to be better at initiating the sensitization than vanilla. Which is a pure olfactory odorant. So we would suggest looking at things which have a combination of olfactory and trigeminal irritant properties as potentially better sensitizers for this particular model.

This increased alpha activity in the chemically intolerant which we did not see in the sexually abused at baseline, has been traced in animal work to certain dopamine receptor activity involvement. So again we have another potential model that could move us into animal studies.

This is evidence that we've had in 2 studies now that we can sensitize heart rate and we can also sensitize diastolic blood pressure during our sessions where these people are exposed to chemicals. We can't right now with our methodology pin it down to the specific acute exposure, we're talking about pre- and post-session. And so whether it is the total package of these sessions or the fact that they're getting exposures during the session I don't know, but just the anxiety about coming into the session does not produce the elevated finding. It is seen in the second session or later on after the exposures have occurred. And so we believe it has something to do with the entire package, but not necessarily to do with anxiety about what's about to happen.

The other point is that anxiety seems to come up the most at the beginning when there's the most uncertainty about what's going to happen. And it's not when we're seeing the group differences.

And that's an important point about sensitization you may see no evidence of it unless you make an effort to elicit it. And so any study that's designed with a one session protocol is likely to miss sensitized people because they may look just like everyone else because of the other environmental factors that are actually hiding the presence of the sensitization.

So finally, we are suggesting a parallel group design rather than cross over design because once you've exposed a person to a particular stimulus that is an initiator, you have initiated the process. And to cross over in a short term study will make it a very confounded study. You have to use at least 2 identical sessions spaced by days to see evidence of a sensitized response. You have to test agents with sensitization potential, not necessarily relying on history of past adverse reactions. This has been a major pitfall in food and chemical sensitivity research in the past. Patient says this, okay we'll put them up there and we'll show that they don't do that. Maybe they don't do it now because they've been avoiding it for 10 years. So you have to take something you think that can sensitize them in the laboratory and do it under that kind of controlled condition. And use sufficiently sensitive outcome measures rather than dichotomous measures, rather than going to the patient and saying do you feel sick or not. At least using some sensitive measures that are highly available within psychobiological research and other fields combining a wide range of approaches including specific biological measures to give us a more sensitive measure of whether the sensitization is occurring.

Dr. Barry Wilson, Chair

Thank you very much. Okay, it's 5 to 5:00, we're rolling. Dr. Sorg, 3 minutes.

Dr. Barbara Sorg

I guess I would consider myself a behavioral pharmacologist coming from the area of drug abuse in general. What I'm doing currently is testing the sensitization hypotheses, trying to develop an animal model for multiple chemical sensitivity and testing the Iris Bell and co-workers' hypothesis.

And let me just explain to you really briefly, kind of back up for a second and explain what a sensitization experiment would be like, so you have a better feel for this. In a rat which is the animal that I use, in a rat model what is typically done is to use drugs of abuse to induce sensitization, so what you do is give the animal a cocaine injection or amphetamine, some of these psycho-stimulants and you see an increase in local-motor activity and that's very easily measured. So we do that, if you give these repeated injections, that is once-a-day usually, or once every 2 days, what you'll see is an augmentation in that locomotor activity so they're sensitized. You can take that animal away from that drug for up to a year, I think Iris mentioned that earlier, and up to a year later put that animal back in the cage and give it the same dose of cocaine or amphetamine and you'll see that the locomotor response is always elevated. So there's a permanent

sensitization and there seems to be a permanent change in the brain that's responsible for that.

Now my studies, I'll just mention one briefly that I've been working on regarding the MCS model and that is taking animals and exposing them to formaldehyde repeatedly. So they are put in chambers and allowed to inhale formaldehyde for 1 hour a day. We've tried this using different doses and different durations of exposure and what we do see is that indeed these animals do sensitize. And by sensitizing I mean that we can give them a subsequent cocaine injection after they've had several daily exposures to formaldehyde inhalation and they do show a sensitized response to that cocaine. And so, even though you ask what does cocaine have to do with all this, we think of it as a probe. It's just a way to challenge the animal and trigger that part of the brain, some of the dopaminergic regions in the brain.

So we see a very robust sensitization and now I'll probably finish here, but we're looking at some other behaviors, I'll just leave you with that, some other behaviors including avoidance to odors. And we do see an enhanced avoidance to formaldehyde as well.

Dr. Barry Wilson, Chair

Thank you Dr. Sorg. Dr. Soreq. How long do you want? Seven.

Dr. Hermona Soreq

I'm a molecular biologist. What we try to do is ask ourselves what can molecular biology methods, or molecular genetics methods offer to improve the testing and the studying of ailments like the Gulf War syndrome.

There was last year an issue of *Chemical and Engineering News* that very much impressed me in that it showed the complexity of stress responses. And that comes just to show us that we definitely need to refer to many systems, not only the brain but also peripheral tissues. Not only our genetic repair, but also the way we respond to stressors.

So let's look at the target, what do we want to achieve and what kind of molecular method can we use. We would like to have a blood test for exposure and risk assessment. And we are studying in our laboratory the cholinesterase gene so I brought that as an example, but any other gene that is relevant would do here. So if one part of the transcript of a serial cholinesterase is up-regulated under stress we suggest to use that as a surrogate marker. Molecular biology now offers two very sensitive techniques to ask if that gene transcript accumulates. One is by amplification polymerase chain reaction and one is by hybridization. Which we can do fluorescently on a single-cell level. So that would be one approach that we would recommend.

The next one is to predict genetic susceptibility. Who might be at the risk for exposure? In that

case we would search for genes that carry mutations that make the individual more sensitive. Again, in our case we found anecdotal information for mutations in the butyryl cholinesterase gene, and more recently a polymorphism in the promoter of the acetyl cholinesterase gene. And over here you see one family pedigree of a Gulf War veteran you might say, in Israel in this case, who was treated with pyridostigmine and responded very badly. And that person is a homozygous carrier of a mutation in a gene that produces that sponge that Dr. Spencer was mentioning this morning. More recently we found a promoter of polymorphism in the other gene in acetyl cholinesterase and over here you see a women who took one pill of pyridostigmine and got very sick for several weeks. So this would be examples for the search for mutations that we recommend to do.

The next aim would be to elucidate mechanisms of delayed pathology. And here we suggest, again being molecular biologists I suppose we are biased, to manipulate the genes of interest by creating transgenic animal models. What we've done in our case is to create transgenic animals that over-express that transcript that we found to be over-produced under stress. And what we see in their brain is a pathology in the axons and neurons, and a depletion of dendrites which predicts insufficient cognition, and insufficient network functioning in the brain. Of course one would like to be able to propose novel treatment strategies. The problem that we've had here is that we've been using a blocker of acetyl cholinesterase which we know helps on the short- term range. The problem is that we've found in our research that that same protein accumulates in response to the presence of blockers. So what we think molecular biology can suggest today is to block production of the protein rather than blocking its functioning. And that would be stopping by synthetic antisense DNA chains that are blocking synthesis, preventing the production of that protein. We are using that technique and I hope to be able to show you tomorrow that that helps the recovery from physical stress to the brain.

Alternative to pyridostigmine, which has been proven good only for a short range, could be by large scale production of recombinant acetyl cholinesterase which is that sponge that can remove the poison away. And our technology for that is to create again transgenic animals that would produce a lot of that protein as an easy source or easier source to produce then the usual human tissues.

And last but not least, we believe that it's important to assess the increased penetrance of drugs into the brain under stress conditions, and for that we have several techniques of choice today for human studies. Computerized tomography, magnetic resonance imaging, and spectral analysis that were mentioned this morning. We are studying a group of patients with neurological indications to try to correlate the intensity of penetrance of xenobiotics into the brain with the intensity of stress responses. Thank you.

Dr. Barry Wilson, Chair

Shorter than 7 minutes. Thank you. 4 ½ minutes for Dr. Spencer.

Dr. Peter Spencer

4 1/4.

Dr. Barry Wilson, Chair

4 1/4. You're on.

Dr. Peter Spencer

Gulf War unexplained illness has provided a wake up call for toxicologists, because we've been forced to address not only the impact of chemical factors, on the nervous system and on other systems, but we have been forced to address the combination of physical, chemical, physiological, psychological etc. acting in concert together at the same time. We've never done this before. We don't know how to do it.

With regard to causation, etiology of unexplained Gulf War illnesses you've heard about progress. It would be extremely nice if we could indeed learn from the Gulf War experience as to what are the associations between these multitude of stressors and the adverse health effects that we now see before us today.

Some have concluded that we cannot possibly do that. Some have concluded that because toxicologists must rely on specific chemical concentrations, etc. etc. and since we don't have those that we cannot possibly begin to make associations between exposures and effects. I think that's a cop-out. To the extent that I think that we've got to be more creative in thinking about how to approach these very thorny and difficult questions.

For example would it be possible to say what was the experience of people who were in the Gulf War exclusively for the Desert Shield period, and went home before combat began. They had a certain set of chemical, biological, physiological, psychological stressors. What was their health experience in comparison with the health experience of people who arrived just before Desert Storm began and who left promptly thereafter. They had a totally different set of stressors. And how do those two sets of individuals compare with people who arrived after the end of desert storm and who were there to clean up the mess. We have in that setting three completely disparate groups of human subjects with, in terms of their exposures to a variety of factors. We could begin to make associations between these three disparate sets.

Now in the combat period for example individuals would be exposed to pyridostigmine bromide, botulinum toxin, combat, etc. etc. Which would be unique to that period. If one of those factors,

or a combination of those factors was so important as to be a driver of MCS, or of unexplained illness, or of fibromyalgia it should emerge.

We spent five years doing a population based clinical case control study in Portland. The Environmental Hazards Research Center funded by the VA. And we find when we do this analysis that we cannot find significant differences among these three groups. Stated another way, we cannot determine differences in the proportions of subjects who have unexplained illness among those who were just there for Desert Shield, just there for Desert Storm, just there for the post clean up, for the clean up period.

The problem with our data is that our sample is extremely small, because circa 10% of individuals among the 700,000 who went to the Gulf were present in those individual three discrete deployment groups. So my specific recommendation is that we call upon the VA, in their nationwide clinical study, to subject the results from that study to the same type of analyses to determine whether or not with a much larger N, whether there really is a difference in the proportion of cases among those three discrete deployment groups. Because frankly, that is the starting point for a toxicologist. If there is no great increase in proportion of subjects who were there just for Desert Storm for example, that should be telling us something about the role of pyridostigmine bromide, for example, which was not taken by individuals who were there just for Desert Shield to our knowledge.

It's a very discrete and specific recommendation. It can be done. We can still learn useful information I believe about compound exposures among these three and perhaps other disparate groups from the Gulf.

Dr. Barry Wilson, Chair

Yep, pretty good. Thank you. Before we move to the next speaker which we will in just one second, I want to point out to you that at 7:30 to 9:00 tonight, the Veterans Forum is an open discussion that is regarding the research priorities where there's an opportunity for veterans to voice their concerns to workgroup chairs. That's one. Secondly is, tomorrow is to be the input to here, so I will ask those here that are very insistent in speaking to us to think about when you want to present the material you want to present.

Dr. Arnold Peckerman

I want to take my time today to tell you about some of the research findings that we were conducting at Santa Romana Hud Research in Eastern New Jersey. It's one of our nation wide centers funded by the VA.

The common theme of the study which I'll tell you about part of it is the ratio within chemical

exposure, traumatic war time stress, and some objective indicators of illness of Gulf War veterans with unexplained illnesses. Next one please.

What we'll be talking about today is the ratio of one of those specific objective indicator illness which is immune system functioning. Next one please.

This is a slide showing the veterans that we've studied, mainly telling that the ones who were studied were Gulf veterans who had chronic fatigue illness. And we will compare them to Gulf War veterans who came back and never had any health problems since. Next one please.

This is a descriptive statistical two study sample showing that we studied 51 sick veterans and 42 healthy veterans and they, and as you can see, they are fairly representative of the population of Gulf War veterans, age and gender composition. And they are similar to each other except on two variables, one of which is education and one is the smoking rate. And when it was appropriate those variables were controlled for statistically. Next one please.

This is the way we see this illness, as a multi-system disorder which is jointly precipitated by exposure to environmental toxicants, and extreme war time stress. Next one please.

To be able to defend this model, first of all we need to be able to show that those veterans who are now sick, they indeed were exposed to chemicals, they were indeed exposed to extreme war time stress, and they do show some abnormalities, so a deviation from the norm that is not apparent in the healthy control group. So this is why I'm showing you that from the examinations we did, we found that veterans who are presently sick that almost 1/3 have post-traumatic stress disorder. Whereas, only 2 percent, actually it was only one veteran in the control group, who also had post-traumatic stress disorder. Next one please.

Now here is some data which is sort of a complicated, but I'll tell you briefly about it. What it's showing you is that veterans who are presently sick, they reported much more frequently exposure to chemicals. They also much more frequently reported being sickened by the exposure at the time that it happened. There were nine different chemicals that we were asking about, and as you can see, almost all of them except anti-tank ammunition, they either reported being exposed with much greater frequency, or they reported being sickened by the exposure with much greater frequency than the healthy group. Next one please.

Therefore, we can conclude tentatively at this point that veterans who now are presently sick with fatigue or illness, they had greater exposures to environmental pollutants, and they were exposed to greater stress during their service during Gulf War. Next one please.

This is the immune data that we collected. It consisted of panel of cytokines which is immune system messenger, and included interleukins-2, -4, -6, -10, -12, interferon gamma, and tumor

necrosis factor-alpha determined in the peripheral lymphocytes, so regards gene expression. Also we measured cell counts for T and B lymphocytes, and cells for markers. Next one please.

This is the result of comparing sick veterans to healthy veterans. What it's showing is that on four of the cytokines, Gulf War veterans who are presently sick had higher levels than the healthy veterans, and that includes interleukin-2, -10, interferon gamma, and TNF alpha. They also had high levels of T-cells with the CD-4 marker indicating those T-helper cells. It's not shown on that graph, but it's showing on the other. Next one please.

So, what we did next, we examined the relationship between these deviations, changes in immune function, and their reports of exposure and stress. For that we used a multiple regression model which tested the effects of the chemical exposures, self-report chemical exposure, and PTSD Mississippi scores on immune function measurements for those four cytokines that were elevated in sick Gulf War veterans. Next one please.

This is the result showing that on all four of the cytokines, that self-reports of chemical exposure and stress explained a significant amount of the variance. Next one please. This graph shows you the individual, the relation between individual predictors, which are chemical exposure and stress, and one of the examined cytokines, interleukin-2. Basically showing that both chemical stress and PTSD scores independently from each other, predicted a significant amount of the variance in cytokine interleukin-2. Next one please.

Now, this is similar data for TNF-alpha showing again a somewhat stronger relationship, but still the same positive relationship between self-reported chemical exposures and present Mississippi PSTD scores and the present levels of this particular cytokine. Next one please.

Similar type of slide again showing the relationship between this time Mississippi PSTD scores and cytokine interleukin-10, and this time showing that the chemical exposure scores were not significant predictors of levels of interleukin-10 in the sample Gulf War veterans. Next one please.

Two of those cytokines, specifically interleukin-2 and TNF-alpha, the interaction term was significant. What it meant is that there were differences between the way stress and chemical exposure scores correlated with this particular cytokine levels, depending on how they stacked up against each other. So, next one please.

And this is the result of those analyses. Basically, we're showing that in those veterans who had low-level of chemical exposures, there were no relationships between their Mississippi PTSD scores and those cytokines, immune function measurements. However, in veterans who reported medium, moderate chemical exposures, and in one of those cases, high-level exposure to chemicals, there was a positive relationship between the present PTSD scores and those two

cytokine levels. Next one please.

This summary concludes these studies, and what is indicated is that Gulf War veterans have altered immune function, and it also shows the specific pattern of changes of what's called TH1-type which might be observed in low-grade inflammatory response to infection, either viral or bacterial. It also shows chronic TH1 activation consistent with major symptoms reported by veterans. We do not know whether if you give somebody these kind of chemicals, they may develop just the symptoms that veterans complain about. Of course, this does not indicate that the relationship works in the opposite direction. And our hypothesis that I proposed at the beginning, that it is supported, that chemical exposure as self-reported by veterans at this time and the stress level during the war predicted certain of the immune functions at the present time.

Dr. Barry Wilson, Chair

Thank you, Dr. Peckerman. We're at 25 after. We started 15 minutes late. Colonel Korenyi-Both.

COL Andras Korenyi-Both

Mr. Chairman, distinguished panel members, ladies and gentleman, my comrades, my fellow veterans from the Persian Gulf War, first of all, let me tell you that I am proud to serve my chosen country into this uniform, and I am talking for you today.

First, I would like to discuss with you the role of the sand in chemical warfare agent exposure among Persian Gulf War veterans. Then, I will intend to draw some conclusions and make specific recommendation to the panel. This work, that work, was done first time in cooperation with the Hungarian Surgeon General who served as a hospital commander during Persian Gulf War in the theater of operation.

For years and years, there was no Persian Gulf syndrome in Hungary. Suddenly, that increment showed up with severe symptoms – even deaths. Ladies and gentlemen, this work was not supported by a grant from any agency. Whoever supported it is sitting there, my wife, she's also a medical doctor and she was not happy about it that I spent the family fortune on it. One of my co-authors, George Korenyi-Both is sitting here and I would like to acknowledge and recognize one other co-author of mine, same name, Adam Korenyi-Both who is a physicist, and I would like to mention Mr. Patrick Eddington, former CIA Analyst who wrote the book *Gased in the Gulf*. You all know about it. He was very, very helpful to me in editing this work. Let me refer back to that book that was distributed to us, *Background Document on Gulf War Related Research*, page 32-33. I was entertained by the language by the way. I regard myself as a free researcher.

" A central question to be addressed by the workgroup: What are the most plausible etiological

hypotheses?" Associated questions: "What are most associated, most plausible hypotheses we are charged to find?" We are charged to find additional plausible hypotheses. If there is any "research methods that need to be developed," and this went on and on and on.

Many possible causes are being investigated, but in a wide variety of duty positions, and differing exposures to the various suspect agents. Investigators failed to identify any common exposure to a single causative agent. So, there is a need to search for a common denominator. That's paramount. Searching for the most plausible etiological hypothesis, we reported previously that the extent to which a Persian Gulf syndrome can be called a discrete condition, rather than a collection of unrelated medical problems, may be the result of a common exposure to the unique sand dust of the Central and Eastern areas of the Arabian Peninsula. Exposure is aggravated often by various other agents attacking individuals whose immune systems are already compromised. This exposure to the Arabian sand is the one common denominator experienced by all service members deployed to the South West Asian theater of operation during Operation Desert Shield/Desert Storm.

We conducted physical, chemical investigations and found that the Saudi Arabian sand is very peculiar with a 5-fold higher calcium content. Close to it is Kuwaiti with 3-fold. The Saudi Arabian sand is significantly smaller than any other sand. The usual sand grain average size is measured in millimeters. The Saudi Arabian sand is from 0.1 to 1 micron, free-floating sand particles. The sizes are the sizes of the viruses. You can inhale down to the target organ with ease.

So, we were privileged to record as a first symptoms of Persian Gulf illnesses and reported by pure luck as a first Persian Gulf syndrome, Al Eskan Disease after the village that we observed. That compromises the body's immunological defense and this is the results of the pathogenic properties of the extremely fine, dusty sand located in the Central and Eastern region of the Arabian Peninsula. Here, I offer to you a pathomechanism of Al Eskan Disease, or called Persian Gulf syndrome.

We deployed approximately 700,000 men and women in a virgin stage of immune system to the theater of operation. Suddenly, they were exposed to that particular sand. Certain psychosomatic conditions were present, but my veterans fellows, it wasn't stress what we had there. It wasn't shooting war. Not for us. For the Iraqis, probably. So, don't try to say that it is in my mind, it is in your mind. That sand caused an immune compromised stage with a pneumonitis – a flu like syndrome. Most of us, there was a complete recovery without any consequences. We deployed 700,000 men. Not all 700,000 men became sick.

There was a smaller group with relapsing pneumonitis or without that, the immune compromised stage advanced, and an immune deficient stage developed. Free-floating silica particles entered the blood stream. Then, chemical warfare agents saturated sand particles, and entered the blood

stream. We had the individual genetic make-up, the endemic infections and adjuvant factors made their roles – seasonal disease, atmospheric pollution, depleted uranium, yes Dr. Durakovic you are absolutely right about it, pyridostigmine, airborne allergic genera, calcium content – ended up in Al Eskan Disease Phase II.

Let me define the dirty dust. The dust becomes a warfare agent when toxic chemicals are micro-impregnated into inert particles. The caprice of "dirty dust" concept that the toxicity of the agent could be enhanced by absorption into inactive particles dates from World War I. Have we been exposed to chemical warfare agents? That's a good question for the debate. In case we were exposed, there are three different ways that, although the Pentagon declared that it had air raided and destroyed Iraqi CW agents' production sites, storage bunkers, by the careful timing, it might have released plumes of CW agents to drift over coalition forces-held territories.

The demolition may have released or direct activity of the Iraqi forces, and I refer to the Jubayl incident in January 19-20, 1991.

Our conclusions are that the physical chemical peculiarities of the sand particles of the Central and Eastern region of the Arabian Peninsula contained a significantly high percentage (18%) of the free-floating sand particles. When the CW agent is micro impregnated into small solid particles of silica, its properties change. Our sensors did not pick up the chemical agents. When the CW agent is in low density, but absorbed by bioactive particles, the submicronic size, the result easily can be misinterpreted as a non-CW agent ailment and could manifest in a variety of clinical symptoms.

Our recommendations are we recommend systemic sand sample studies to detect CW agent contamination from areas under suspicion of being saturated by CW agent from the theater of operation. Additionally, to the presented evidence of CW agent presence in the Kuwait theater of operation, and the ways of sand saturation and production of "dirty sand," to further support the general thrust of this elaboration, research needs to be conducted to detect CW agent breakdown byproducts in the collected sand samples. Testing the presence of antibodies in our veterans is very important. We recommend the study of the neuromuscular junction by muscle biopsies of symptomatic of Persian Gulf War veterans by histochemical, electron microscope, and cystochemical means for detection of the pathomorphology of low density exposure to cholinesterase-inhibiting chemicals. We recommend to accept Al Eskan Disease as a plausible and preeminent elucidation in the preponderance of Persian Gulf War illnesses.

My presentation is exactly 7 minutes and 15 seconds, sir. Thank you.

Dr. Barry Wilson, Chair

Well, that's your watch, sir. I said that we would end at 10 of. We will. We are compromising

the idea of getting recommendations for future research down here. Some are coming out. I will ask each panel member to prepare a list of their recommendations, give that to me, they will be typed up, and then we can hand out and be able to proceed with that. I will ask members of the audience that tonight and tomorrow are the times where there is input, and I will now move on to our next speaker.

Dr. Claudia Miller

All right. Four minutes – a challenge. There's a theory of disease that has emerged in the last decade and it involves exposure to toxic agents that, in a sub-set of people, induce loss of tolerance, many of the chemical, food, and drug intolerances that you know the veterans have. This has emerged because in studies in more than a dozen countries, after people have been exposed to organophosphate pesticides, solvents, sick building environments (like the EPA building) – initial exposure event occurs. A sub-set of people, not everyone, not everyone develops allergies either, a sub-set of people lose specific tolerance for previously tolerated chemicals, foods, drugs, alcohol, and caffeine. Subsequently, you have a sensitive individual who, when re-encountering common, everyday substances, are now having symptoms and they are being triggered by these common substances.

Veterans who had no prior difficulty drinking caffeine, having one or two or five beers, now report being very sensitive to one or more substances. The symptoms are those of fatigue, memory and concentration difficulties, changes in mood, and multi-system symptoms. The physicians come along here in their Titanic, see the symptoms, and formulate a diagnosis based upon the symptoms – not aware of what has gone on before. It's only because we've had now, large exposure groups in all kinds of countries, that's telling us that this process is going on.

The specific mechanisms remain to be determined. It may involve neurological sensitization. It may involve changes in receptors. We don't know. But there's a general process based upon phenomenology observed in many countries at this point by different researchers. The unique thing is people aren't just reporting chemical sensitivity, they're saying they cannot tolerate foods that they used to enjoy – pizza, beer, and a variety of other substances that people like to have. There's not much secondary gain there. Giving up chocolate is not something I would like to do, anyway.

The fact that people have now multiple intolerances, this is called "masking." If they are sensitive to multiple agents, then when they're exposed to any particular one, they can't even tell what's causing their symptoms because there's so much background noise from responses to so many different substances – whether it's diesel exhaust, foods they're eating, medications they're taking – that they cannot determine what is triggering symptoms.

The idea has been, and proposed now in the last 10 years, for more than 10 years, that people

need to be placed in a controlled hospital environment. All that means is, not in a sterile environment, but one in which you've reduced environmental chemical exposures to as low a level as practicable. So, the goal would be then, to take people who have multiple, overlapping responses to common, everyday exposures, place them in a controlled hospital unit, allow their symptoms to play out. Patients who have gone through this process report feeling better than they can remember. At that point in time, you can go back and do double-blind, placebo controlled challenges. For example, with caffeine using a blinded tablet versus a non-blinded tablet. Very simple and direct approach that has been recommended now by several federal agencies in more than four meetings in this country, and some international meetings as well.

Dr. Barry Wilson, Chair

Dr. Ashley, how much time do you need? Two minutes?

Dr. David Ashley

I just really want to make one comment. I work in the National Center for Environmental Health, and what we have been doing for a number of years is hearing anecdotal reports of people expressing symptoms, and current concern about chemical exposure. We will go in and do epidemiologic studies of those, and those studies usually don't show a whole lot. They don't show what we expected to see after the anecdotal reports.

And, over the years, I've come to the conclusion that a lot of this is due to genetic differences – differences in genetic susceptibility where you have some portion of the population that has a certain genetic make-up that makes them susceptible to these things. And the one thing I'd recommend that we continue to do, that's been kind of suggested by others, is that we look at genetic susceptibility in Gulf War veterans and see if we can distinguish why there are certain veterans that are showing such extreme symptoms and other veterans that are not.

Dr. Barry Wilson, Chair

Thank you. I want to remind the panel, future research, write it up, give it to me tomorrow. As soon as Dr. Abou-Donia is done, there will be a few minutes for questions.

Dr. Mohamed Abou-Donia

Thank you, Barry. It has been a very long day. From listening to everybody, I think that there are three major questions we need to answer. One, that I think Dr. Spencer mentioned earlier today is, is it possible that exposure to low-level chemicals, below the threshold level that would cause acute effect, would this exposure lead to neurotoxic effect or neurologic problems? This is a very difficult question because it depends on the intrinsic toxicity of the chemical, depends on

whether we have multiple chemical exposure or just one chemical, and also as we heard depends on the sensitivity of the individual.

The second question is the delay period. Is it possible that there would be such a delay period after exposure before the onset of clinical signs? Also, is it possible that the disease would continue for years after the first exposure? That we need to answer.

The third question which I think would be very significant is the prognosis. What is the prognosis for those who have been exposed and have the disease? Is there hope that they might recover? Or what exactly do we expect?

I think these are three questions that we need to address and we need to, hopefully, devise proposals to study these questions. Thank you.

Dr. Barry Wilson, Chair

Okay. We now have a few minutes for questions. Please, go stand by the mike. How many people want to speak? I don't want to shut anybody out, but I also don't want to shut them out of dinner? How many people want to speak? The ones in line? Okay. Please, then, we have 5 minutes. Can you each take 2 minutes, ask or do what you gotta do, and remember, there's time tomorrow. I'll try to get everybody.

John Rossi, PhD
Office of the Chief of Naval Operations
Washington, DC

I used to be formerly the Scientific Technical Director of the Navy Toxicology Program in Dayton, Ohio. There are two things that I want to say. First of all, I've found so far today this meeting to be the most total waste of time. I've learned absolutely nothing here, and I don't see how anyone could have possibly determined that we are actually making progress toward the actual charge of this thing of coming up with new research areas. Enough of the politicizations.

One of the things that we've continually heard today, and I think it hasn't necessarily been explicitly stated, but there seems to be a lot of bashing of the DoD. And, what has not been said at all is that we have a comprehensive plan for looking at deployment toxicology situations. We have a deployment toxicology assessment program which we've worked out a master plan for, we have a 30-year plan for doing neurotoxicological risk assessment. Now, this is for prevention of another set of instances of Gulf War illness. But, it's something that the military is actually actively doing.

What we've done is, because of the Congressional money, we have been taking it out of our own

hides, we've been working this program basically out of medical R & D money from Army and Navy sources. You know, I just thought that it would be necessary to say that. Now, there's been a BAA. We've been identified as the laboratory at Wright Patterson Air Force Base that people are encouraged to collaborate with. Most of the people that know my stuff, it's basically animal models, but we're starting into the human stuff. We're in collaboration with the VA in Dayton right now. And so, anyone that actually has some interesting ideas, I'll be glad to speak to them about collaborating on the VA level.

Dr. Barry Wilson, Chair

7:30 tonight. That's where the beef is. Next.

Dr. Kathleen Hannon
Orlando, Florida

I'm a radiologist, and I'd like to tell you about a sub-set of patients that never made it to the Gulf War, and they're sick. And I know several of the patients. One of the people that's here right now, she never stepped foot in the Persian Gulf and she's sick, and the common denominator is the vaccines. I want to tell you about experimental adjuvants, but first I want to tell you about alum. Alum does not produce T-cell responses. Here's an article from *Syntax*. Antigens do not produce T-cell responses. Experimental adjuvants produce T-cell responses. Look at this, squalene elevates IL-2, what's the other one that you mentioned? IFN and TH-1, they're all in this article.

Would you like to know what squalene does? I can tell you. I can personally tell you. What it does is you flunk the PET scans of your head, you flunk the brain SPECT, you flunk your EMGs, you have positive skin biopsies, and you get elevated IgGs, as well as chronic fatigue.

Gulf War syndrome is just not chronic fatigue. It's big-time autoimmune disease. If you took a poll, there are a lot of people out there with lupus. And I think that, from now on, it should be vaccine, the vaccines should be studied. The experimental adjuvants should be studied. Thank you.

Dr. Barry Wilson, Chair

Thank you ma'am. Okay. Two minutes, please. At 7:30 tonight, there's an open mike, and tomorrow. You go now, sir.

Richard Wadzinski
Veteran, United Veterans of America
Godwin, North Carolina

I'm an Air Force retiree, Gulf War vet, 150% disabled by the VA's ratings. My first thing is that, Dr. Spencer, that we don't waste research money, when you say using Shield/Storm in mop-up crews, you need to add a fourth group – vets that were there the whole time. It's hard to just put, you need to add a fourth group to that. Then in the top, on all this research, I went to the Registry, and I was never heard from again. My liver quit, I almost died, got a transplant, and I've got many other signs and symptoms of this Gulf War stuff and no answers. Let's put the money and research to good use. They need to do something with the veterans.

Dr. Peter Spencer

I agree absolutely. Good. We did add that fourth group, and that's right on the money.

Dr. Barry Wilson, Chair

Thank you, sir. Let's get to future research in this meeting in the next two days.

Dr. Leslie Simpson
Red Blood Cell Research Trust
Dunedin, New Zealand

To what extent, as the panelists have told us today, help us to understand why only about 12 percent of the troops suffer from the problem. What have we learned which will help us now to understand in vets in whom no abnormality can be demonstrated, they are still sick people? What have learned which will help us to understand why the French military forces do not have a single case of Gulf War illness.

Dr. Barry Wilson, Chair

Thank you, sir. Next. Before you go, let me just take the liberty of making a funny response, but a quick one. You can have a lot of your muscle, maybe as much as 50 percent, Dr. Spencer might disagree, damaged, and you never find it out until you try to do a marathon because not all your muscle is working at once. What if we all have a lot more damage than we imagine, and if we tested right, we could find it out. Yes, sir.

Stephen McFadden
Independent Research Advocates
Dallas, Texas

To assist in research, it would be useful to have a library just like EPA has a Pesticides Dockets Office, or if we went up to National Library of Medicine, we could go in a backroom. There's probably a hundred research proposals funded so far. There should be a hundred research

proposals there, a hundred study results, all of your papers should be there. If somebody wants to seriously research it, if you had one library somewhere, this would extremely assist the research. How about National Library of Medicine in DC?

Dr. Barry Wilson, Chair

You got it. A Gulf War library. Thank you very much. Okay, is this the last one?

Dr. Beatrice Golomb
RAND Corporation
Santa Monica, California

A couple of comments. One regards the cytokine profile, there was actually a hypothesis paper in *Lancet* that predicted that there might be shifts towards the TH1 profile and pointed out that some vaccines, including pertussis, which was used as an adjuvant by the British, but not the U.S., and some other adjuvanted vaccines, as well as pesticides and stress might be expected to produce such a T-cell cytokine shift.

And, the other comment regards Dr. Somani's research, and I just wanted to point out that there's been a lot of criticism of some of the animal research on the grounds that they've used high doses of the chemical pyridostigmine bromide. But, in fact, if you look, for example at monkeys, the studies that show efficacy used 20 to 50 times higher doses because those are the doses that are needed to produce the comparable level of acetyl cholinesterase inhibition in monkeys compared to humans. So, we need to be careful what we call the equivalent dose. Is it the milligram per kilogram equivalent dose? Is it the acetyl cholinesterase inhibition equivalent dose?
And also, on a related point, pyridostigmine bromide decarbamylation isn't the only time course issue for PB that's potentially an issue. Pyridostigmine bromide also causes direct desensitization of the acetyl choline receptor and causes a variety of other down-regulatory effects that can lapse after the PB has decarbamylated. So, I really think it's important for additional research to look into the time course of those multiple other neurophysiological effects.

Dr. Barry Wilson, Chair

Did you have a short comment? Because I didn't see you there earlier.

Denise Nichols, RN, MSN
National Vietnam and Gulf War Veterans Coalition

Short comment. I'm going to remind you all, we vets here are listening. And I'll tell you what, there's a lot of frustration building in your vets. You don't seem to get it. This is really

uncomfortable for us. Look at this man, how young he is. Okay. We were very healthy when we went. And we're going down fast. Somebody, I think, said 30-year research. Forget it guys. We need help now. We need the SPECT scans now. To every vet out there that's identified themselves, okay, research is one thing, but lifesaving and maintaining our quality of life is another.

Please, please, look at what you're doing. Did I hear this right? Thirty years? Think again. We're all going to be dead. I know everyone is dying slowly in this room, whether you're vets or not, but this is about the quality of our lives, and I don't think the researchers have got the message yet. You've got to move faster. You've got to get our SPECT scans done. You've gotta get things out there at every VA hospital or somewhere for us. Thank you.

Dr. Barry Wilson, Chair

7:30 tonight. Remember, you're preaching to a smaller choir here. One last comment, please, if you're standing.

Audience Member

This is really a question. I'm wondering how this meeting was conceived to only deal with chemical effects that may have induced Gulf War Illness and has essentially omitted the physical – the vaccines, the possible electromagnetic fields that were experienced. Could someone explain to me whether there is going to be another forum where those potential exposures are going to be discussed, or do we need to steal time from the chemical exposures and discuss those here?

Dr. Barry Wilson, Chair

First off, I cannot explain. We are invited and it was designed. Secondly, it says Pathophysiology, that lets in a lot of other things. We were asked to emphasize chemical exposures, and your comments, I think, tonight, would be very good, too.

I'm going to have to close now, but I am reminded of the Canadian national game. I went to a fight and a hockey game broke out. Can we disagree without being disagreeable? Except for disagreeable guys like me. I try my best. I want to thank the audience for your patience, your opinions, and we'll hear more of them. And then I want to thank the panel. I want them to have been listening to how we get on about our business.

The session was adjourned.

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Day 2 – Monday, March 1, 1999 - Morning Session

Dr. Barry Wilson, Chair

This is the pathophysiology/etiology workgroup. This is the input time. We also have a particular piece of business to do. If I look up tight about it, it's because our charge is to make research recommendations on pathophysiology/etiology mechanisms. I have put it very simply to all of us. We're charged here to try to figure out what happened, how it happened, and then know what to do to get rid of it. It's that simple.

Last night, I sat and listened for three hours to so many stories, so much pain, that I know that all of you that were there and listening too felt. I don't want to see our time wasted in this session, the workgroup session, when all who spoke, and some of you were in this room last night, wanted us to do something – please help us do something by restricting you remarks to research recommendations. If you want to holler at me, I'll be the target. I'm not stopping you. If you want to engage in saying that this is turf war between the different agencies, I didn't bring a lawn mower. But I did bring a weeder. I've got to weed out public comments, scientific comments, to get to the recommendations. Please help us help you. Those of you that are on the list, if you put yourself on the list before last night, don't do any of that over again here. I will rule you out of order. I'm going to the audience to help us to get our work done. Thank you.

What I would like is first to show this to you. Then, Dr. Bill Suk will be handling the flip charts, Dr. Sheila Newton, the screen, and our approach will be to accept research recommendations. Now you've signed up, but those of you that didn't have research recommendations, please, let it go for the sake of all of us – for the team.

What I summarized here are in two forms. There is the notes made by Dr. Newton that gets us towards recommendations here that she pulled out of what we said yesterday. There are my own block diagrams of this, and it was pointed out to me that I left out desensitization. I did not mean to. To get us started to block out some work, and I didn't realize it until I came to this meeting, because each of us have telephoto lenses in our areas of research, I'm cholinesterase's biomarker. Some of the work that has come to the level of hypothesis testing – we could break it out in that. The stress, immunity, sensitization, MCS, TILT, gene expression, low level chronic exposure -- part of the level of hypothesis testing research where we could make recommendations. Another whole area is biomarkers - early warning signs. Boy, if I could sniff my way to knowing when there's a problem, it really would be very good. Chemical sensitivity is there, stress, chemical agent exposures. We need early warning signs.

I'm putting on the list of data gaps, as the other kind of block of recommendations we could

make, the depleted uranium. Last night was very much an eye opener for me from the testimony of veterans. And if any of them that did talk about DU last night are here, thank you. It's on my list big time.

The central nervous system data gaps will always be there. There's a lot going on in our heads and we must understand it. Environmental factors. Sand is one of them. But sandblasting isn't all. We've got many environmental factors. It's a category. Twice now we have asked for a Gulf War library. Maybe it's not a research recommendation, but some group has to recommend it. I'd like it to come from here.

To get started, the panel, I've asked if you would prepare some recommendations, and it would be a good time to turn them in to Dr. Newton now so we can have them for this afternoon when we really hammer out our recommendations. As far as I'm concerned, it's starting now from the way we're going. Somebody gave me a recommendation for further research from Kim Pagels. He represents approximately 1,000 Danish Gulf veterans, and he recommends research into gastrointestinal problems, skin rashes, mental reactions of staying in the Gulf area. So we can kick that off, and I'll give it to Bill for him to paraphrase.

Okay, I'll read this one while someone on the list is getting ready to come forward. We can cross off Bob Haines. He says to have DoD and CDC determine if Soviet-made Iraqi weapons located throughout the U.S. in National Guard camps are completely free of any biological weapons. Are they clean? If they aren't then decontamination procedures should be initiated, and the public may be at risk. This is not quite a research thing, but it is, if it's raised it's raised, and now it's short. Okay. Now, who wants to first give a research recommendation? Okay, why don't you get by the microphones and stand back there. And then, if you give your name, Sheila will cross them off.

Dr. William Morton
Oregon Health Science University
Portland, Oregon

The thing I want to emphasize is the fact that so many people here are interested in multiple chemical sensitivity as a model. The big issue with multiple chemical sensitivity is that there has been no laboratory test to document it. I think that's inhibited research. One thing that we've noticed in our clinic, our occupational health clinic in Portland is that in over 100 individuals with multiple chemical sensitivity, over 90 percent of them have evidence of porphyrinopathy, porphyria. The reverse of that is that over 90 percent of the individuals with porphyrinopathy have symptoms of multiple chemical sensitivity. This is a very strong congruence. I think it's stronger than anything we've heard so far presented here. This would represent a marker for MCS that doesn't now exist.

Dr. Barry Wilson, Chair

Okay. Would you explain porphyria for the audience so we don't all sound like we're physicians looking up the Merck Manual?

Dr. William Morton

Okay. Porphyria is a group of generally hereditary enzyme deficiencies which are associated with, sometimes with symptoms. About 60 percent of these are subclinical, but in the presence of certain initiating exposures usually, people develop symptoms, and the symptoms are usually neurologic or psychiatric. By neurologic, I mean to include autonomic as well.

Dr. Barry Wilson, Chair

Thank you. I'm going to have to ask folks to see if you can do it in 2 minutes so then we can really talk to each other as we work these recommendations out. Sir.

Craig Stead
Putney, Vermont

I'm here to talk about the oil fires and petroleum and research recommendations. I won't talk about the fires and petroleum. We know they exist. We know there were exposures. The exposures are inadequately characterized. And we know the symptoms of Gulf War illness fit the pattern of an exposure to the two toxins, soot and petroleum. My specific research recommendations are characterize the oil rain and other petroleum exposures, both relative to the composition and the concentration. Characterize the soot exposures. The characterizations done to date by the DoD are inadequate, I believe, relative to what was actually experienced. You need to assemble the known literature on petroleum toxicity and toxicology looking at the organs affected, the symptoms, and the delays of symptom expression. You need to look at the known methods that are out there of diagnosis and treatment for petroleum exposure, both inhalation and ingestion. And the final research recommendation I would make is that pulmonary function testing, specifically FEV_1 which is forced expiratory volume in one second should be done yearly on vets who are expressing an asthma or pulmonary symptom. Thank you.

Dr. Barry Wilson, Chair

Thank you very much. That's the timing. That's the drill. You did that very well.

Maggie Eklund
Promotional Director
Desert Storm Justice Foundation

Oklahoma City, Oklahoma

I'm just here giving a proposal from Dr. George Chako in Oklahoma City who is the Medical Director and Department of Neurology and Nuclear Medicine physician. He has done quite a bit of SPECT imaging on veterans and already found some alarming data he hasn't seen in the civilian population. He has a proposal here about the direct relationship between cerebral blood flow and of regional central metabolism that has been proven in epilepsy and dementias, and he thinks we should target some of this in a pilot study of doing both PET and SPECT, and go into further research, even if it's multi-center. If any of you want to find me, any of the toxicologists or anybody, he would like to have me give them a card so that they could share information.

So, really, brain SPECT imaging for neurodegenerative disorders in Persian Gulf veterans needs to be investigated.

Dr. Barry Wilson, Chair

Thank you, Maggie. It's on the screen already. Next.

Dr. Vinh Cam
Presidential Special Oversight Board for DoD Investigations
of Gulf War Chemical and Biological Incidents
Greenwich, Connecticut

My comments are brief. I would like to see 3 things. One is to do more immunotoxicity tests of Gulf War veterans. I am talking about human trials, human testing. The second thing is, when you have a chance to do clinical trials, try to do the same tests to monitor these patients before and after to be consistent. My third thing is synergistic effects of pesticides. And my general comment is, I really urge all the scientists to look at cellular level. I personally feel there isn't enough effort to look at that. Thank you.

Dr. Barry Wilson, Chair

Thank you very much. And as a guy that studies pesticides, I have to say – you bet.

Cynthia Wilson
Executive Director and Chairman of the Board
Chemical Injury Information Network and
Environmental Access Research Network

I have two recommendations. One is to look at the sex bias in chemical injuries that seems to favor women, and there may be a clue in why women appear much more vulnerable to the effects

of toxic chemicals. The second is the fact that we may be looking at more than one illness or more than one thing going wrong in people who get sick. For example, my organization believes that it takes three separate things to make up MCS, and all of it has to come together at once in order for anybody to get sick. So, there may not be a single mechanism to account for all of the symptoms you're seeing in everybody. We may be looking at multiple mechanisms overlapping and creating the illnesses.

Dr. Barry Wilson, Chair

Thank you very much. Three, huh? It takes tow to tango, but three to get sick. Could you put the pesticide part on the one with the immunotoxicity – to look at pesticide interactions?

Edward Bryan
Malden, Massachusetts

I'm a firefighter. Totally disabled. Both as a Gulf veteran and a full front line firefighter here in the United States.

Dr. Barry Wilson, Chair

I remember you speaking last night. Your recommendations, sir.

Mr. Edward Bryan

I would like this body here today to really look at the oil well fire exposures. They were devastating. I can't say that anymore. The oil well smoke and soot -- we should have been wearing respiratory protection. It should have been ordered first hand. Number 2, I want every Gulf veteran to have SPECT scans. I don't care about a dollar value. There shouldn't be a dollar value placed on this. Number 3, the lungs aren't being looked at. They're not being washed. There's a test out there that they can wash them. That has not been addressed yet. That goes along with the PFT testing. Number 4, carbon monoxide exposure. They see that on my brain. I bet you every one of my Gulf veteran cohorts have the same identical problem, could have the same problem as the blood flow that the neurologists look at. I want 100 percent recall for all the troops through your social security numbers. I think that has to be addressed.

Dr. Barry Wilson, Chair

That's a different area. That's isn't quite research.

Mr. Edward Bryan

Well, I mean, your body can issue that.

Dr. Barry Wilson, Chair

You said that last night, though.

Mr. Edward Bryan

That's all right.

Dr. Barry Wilson, Chair

But we're the same people here. We don't need redundancy, we need new ground.

Mr. Edward Bryan

Our families have to be protected. God forbid, if I died, that's another issue.

Dr. Barry Wilson, Chair

Sir, I'm all on your side, but we're for research recommendations, and I said I was going be tough.

Mr. Edward Bryan

That's all right. No problem.

Dr. Barry Wilson, Chair

Thank you. You got that recommendation out last night, and we heard you.

Mr. Edward Bryan

But a lot of people weren't there that are here today.

Dr. Barry Wilson, Chair

I wish they were.

Mr. Edward Bryan

Thank you.

Dr. Barry Wilson, Chair

Thank you very much, sir.

Dr. Thomas Tiedt
Long Boat Key, Florida

It looks like we're setting out on a new course of, on a new round of research, and I would like to recommend a few things just with some perspective, and directly falling from the panel's chair, a comment yesterday about some sort of foundation in the past, and particularly Representative Sanders' comment, "let's move the ball." There's a long history in a lot of these areas. I know I'm a cholinergic person. Certainly, the very exciting stuff I heard from Dr. Soreq yesterday and this morning, and Dr. Abou-Donia, I remember having detailed, in depth discussions about it at journal clubs in the 1970s. A tremendous amount of work has been done that there continues to be a denial about, and it leads to a lot of presumptions that I hear that are, frankly, incorrect. "PB does not cross the blood brain barrier" and "PB is not harmful in myasthenia gravis patients" are very incorrect. A second recommendation is that . . .

Dr. Barry Wilson, Chair

What was your first?

Dr. Thomas Tiedt

That we look at the research that's been done. Frankly, there are thousands of studies directly relevant to Gulf War.

Dr. Barry Wilson, Chair

Okay. Bill, "take a hard look at cholinergic research." Second recommendation. I'm being rough.

Dr. Thomas Tiedt

I understand. The second is to look at what we do in our research do loop. We all apply for research grants, and in the proposal, we emphasize how important this particular research study is going to be, how critical, the data is going to really answer some questions. But then, we arrive at meetings like this, an inch document gets put together, and study by study by study gets castigated as being full of flaws and unusable to anybody. I really think that doesn't serve any of

us. Finally, I would hope that we would renew our commitment, to ethical principles involved with research, both on the animal side, why do redundant research, and certainly on the clinical side, we should not endorse the idea of something that's been disproven, for example. PB is not a chemical warfare agent protectant, atropine is. Certainly in the journal clubs and directly out of Dr. Soreq's comments this morning, we know that there's synergies with OPs and "reversibles." So, we have some Nuremberg Code problems and other ethical issues.

Dr. Barry Wilson, Chair

Thank you. Next.

Dr. Ruth McGill
Psychiatrist
San Angelo, Texas

I have 60 pages of recommendations. I'm going to skim it down into 5 quicky titles. Delete research into psychiatric diagnosis and psychiatric correlation with Gulf War syndrome. They are independent and our state-of-the-art of psychiatry is not up, it's not adequate to reach the correlations at this time. Eventually, yes. Now, it's trivial. It's irrelevant. Three quarters of funding in the future should go to patient treatment studies – treatment outcome, treatment possibilities. We do have the technology to do this, and it is the only compassionate way to direct our resources. Look in the ICD and change our concept and terminology for multiple chemical sensitivity to chemical hypersensitivity, which was the original statement, the original ICD term 50 years ago. MCS is a political term. We should go back to chemical hypersensitivity. Look at the research on cholinergic activity of the pupil. This absolutely cannot be faked by a patient, and it's been very promising in Alzheimer's. It will point to cholinergic damage in our veterans. I'd like to consolidate my own approach to cellular energetic deficiencies and blocks. I propose that as a unifying field theory to bring together the chronic, progressive, inflammatory, degenerative, metabolic, nutritional – all of these aspects of the Gulf War illnesses. Also, go to multiple organs, multiple systems, consolidating. Thank you.

Dr. Barry Wilson, Chair

You're welcome. Next.

Dr. James B. Lucot
Associate Professor
Wright State University
Department of Pharmacology
Dayton, Ohio

I originally signed up because yesterday's list did not have stress as an interactive factor, and I'm very glad to see that it's back on. I've got some data suggesting that stress impacts the MPTP model of Parkinson's disease. So, I would make as a research suggestion that the interactive studies look for pre-morbid indicators of delayed neurological deficits.

Dr. Barry Wilson, Chair

Okay. Thank you. Did you get that? I think you said it kind of fast. Would you repeat your bullet for Sheila.

Dr. James Lucot

Apparently there are going to be some . . .

Dr. Barry Wilson, Chair

No, don't elaborate. Just give us the name.

Dr. James Lucot

Pre-morbid indicators of delayed neurological disorders – Parkinson's, Alzheimer's, whatever.

Dr. Barry Wilson, Chair

Thank you. Next. Let's see, who is signed up? Oh, the gentleman from New Zealand, now do you want to speak? Two minutes. Same time.

Dr. Leslie Simpson

I would like to make a recommendation that further work that I have been doing concerning the red cells of people who have the symptoms of Gulf War illnesses in Australia, Canada, England, and the States needs to be investigated and pursued. I am using a scanning electron microscope-based study of the red blood cells. The current textbook study of the red blood cell is unsustainable, and the evidence of this goes back to 1970. I need 5-drop blood samples immediately fixed from as many vets and from non-participants as possible to cement the problem that the primary problem of the vet, the one which explains the various symptomatology, is a consequence of poor blood flow due to changes in the cell.

Dr. Barry Wilson, Chair

Thank you very much, because you spoke earlier, and you spoke now, and you've made your

point well. The timing is perfect. Dr. Baumzweiger, you want to present your recommendations, briefly?

Dr. William Baumzweiger
Physician, Cedars Sinai, UCLA
Studio City, California

What I suggest is that there be improvement in the neurological evaluations so that the VA and DoD neurologists learn a good cranial nerve exam. All these people have abnormal cranial nerves. I'll be glad to provide you with the cranial nerve examination – how to really do it. None of them do it right. It's true. They don't even bother.

Secondly, I really recommend that they do very good lymphocyte testing and testing for reactivated viruses and funguses, because you'll find that there's a 50 percent abnormality rate in T-4/T-8 ratios in Gulf War veterans which is so out of the statistical probability range as to be extremely significant. The chance that it is just a fluke is vanishingly small. So, these people have immune problems as well as neurological demyelinating problems.

They all have to be tested for the EEG abnormalities that we were talking about yesterday with multiple chemical sensitivity, that is, increased alpha waves is what you see. They all have to be followed by EEG and EMG for whatever treatments, because you can see improvements in the EEG and in the EMG. And there is a treatment protocol which I just gave to the treatment group which I have developed over four years. Thank you.

Dr. Barry Wilson, Chair

Thank you very much. That's Dr. William Baumzweiger, and he has some things to hand out.

Dr. Peter Spencer

Barry, I'd like to ask for a brief explanation of what these cranial nerve deficits are.

Dr. Barry Wilson, Chair

Oh sure. Please.

Dr. William Baumzweiger

If you look, first of all, in the olfactory nerve, olfaction, there is, and it's true for all of them, at very high levels of stimulation, the nerves actually go into hyperactivity and you get people having severe olfactory and visual, including cranial nerves and light reaction, kind of reactivity. The

same thing is true for hearing. Loud sounds bother them. On the other hand, they can't hear soft sounds. They can't smell slight scents. Their convergence reflex disappears at more than 3 or 4 feet. They start to see double. They see double up close because they are hyper-converging. They see double at 8 feet because they lose their conversions. But no one tests for this. They're losing the sensation on their face. They can't localize sounds. This kind of thing. All right. Does that answer your question?

Dr. Barry Wilson, Chair

Okay. Next. Okay. If there are no others, okay, is it a recommendation? Because I'm going to move us into hammering these recommendations out with you guys as partners.

Dr. Richard Graveling
Head of Ergonomics
Institute of Occupational Medicine
Edinburgh, Scotland

I'll keep it as brief as possible. I didn't sign up. But I think it is important. We had the comment from Cynthia Wilson about more than one illness, more than one mechanism. We've heard a lot of comments about exposures to widely differing things, certain petroleum, vaccines, insecticides. There's a strong possibility here, from my readings of the MCS research, that we are looking at different groups of people with different disorders. We need to be very sure, in whatever research you carry out, that you are studying the same people because otherwise you'll get conflicting results which will lead to dissatisfaction and scientific lack of acceptance. So, you need to make sure you're studying the same people, you do need to look at the definition of the groups of people that you're looking at. Thank you.

Dr. Barry Wilson, Chair

You're welcome. Is there someone else who wants to speak to a recommendation? Okay.

Rick Hirst
Training and Quality Control Specialist
Veterans of Foreign Wars – Washington Office

Yes, sir. I was part of the panel yesterday on the veteran's organizations. After listening to some of the veterans at the forum last night discussing depleted uranium, we, as an organization, would like to see additional research done in this area to include not only weapons handlers, but munitions plant workers and white collar people in the plants who have incidental exposure. That's one thing we would like some research done on.

The second item would be the relationship with amyotrophic lateral sclerosis. As I said yesterday, our information tells us that it's significant. Not that it's causal, but that it is significant. When I discussed this with certain officials within the Department of Veterans Affairs, I was told that they were examining it also. They thought enough to bring in several experts to Central Office to discuss this, and I've been told that their findings do not support a relationship, but we would like some independent research done.
The last item is, of course, birth defects since the federal government has never considered paying birth defects prior to spina bifida with Agent Orange involved veterans. It's something I don't think they think of as part of their responsibility, and something that they probably do not have the expertise in. Thank you very much.

Dr. Barry Wilson, Chair

Thank you. I think they've done the epidemiology on the birth defects, but if it needs to be looked at again . . . It's on our list. Second, I took the chairman's prerogative after last night of putting depleted uranium on.

Mr. Rick Hirst

I attended the workshop yesterday on assessment and there was really interesting information that one of the doctors gave on pregnancy.

Joseph Miller
North Carolina National Guard
West Jefferson, North Carolina

My main concern is the same concern he had just a minute ago. I was assigned to the 1450th Transportation Company, and I'm a Desert Storm veteran. My main concern right now is the birth defects. I understand the government study with the 70,000 records that were checked, and we found seven with the Goldenhar's syndrome. I don't know what the world or a national average is on Goldenhar's syndrome. My understanding is it's something like 1 in 400,000. In the government sponsored study, we had 7 in 70,000.

Dr. Barry Wilson, Chair

Okay, if you want it to be reopened, it's on the list.

Mr. Joseph Miller

That's not the problem. I want it looked into.

Dr. Barry Wilson, Chair

Okay. Your point is made. Okay. This may be the last, because folks aren't jumping up.

Dr. Arthur Hume
Professor
University of Mississippi Medical Center

Over the past 3 or 4 years, I've tried to do research on Gulf War illness without being able to get funding.

Dr. Barry Wilson, Chair

We can't recommend that, sir.

Dr. Arthur Hume

You killed my point. My recommendation was that you give me some money to do some research. But that's not my point. I don't see too much on causative agent detection. I know it's a big fight, that's one of the things about it, causative agents and what happened to several other causative agents, even though I was also alarmed last night with the uranium, the use of. But, we've been interested in the overall picture of causative agents. The scientific approach of detecting a causative agent would be that you have the symptoms, epidemiological studies, and then you have the agents that you wish to consider. So, I don't know whether maybe I'm out here in the woods, Mississippi is that a way a pretty good ways, and we're boondockers in many ways – but not this. But, we've had no information on epidemiology like you'd like to have.

Dr. Barry Wilson, Chair

All right. That's a different session.

Dr. Arthur Hume

This is a recommendation.

Dr. Barry Wilson, Chair

I know, but there's a different session for epidemiology. You can hit them twice. Seriously, we're on your side.

Dr. Arthur Hume

Do I need to go to that other session and do that?

Dr. Barry Wilson, Chair

Why not? Thank you. It's included here, but I'm saying, you may need to talk to them. Now, first, I have the utmost gratitude for this audience because you're helping us to get on now with our business of deciding. The first set up there was just a block of hypothesis testing, biomarkers, data gaps. Does that categorization work for us? Or do you have another large category you'd like to see, as big as those three? Because, if those categories work for us, then there are two roads we could take. One is to have some people volunteer for each of those areas so we're working up some subgroups that will be presented this afternoon. I'm really trying to expedite.

The second is to fill in some of that now, between now and noon, and still get some volunteers for some work groups so we can start really moving it down the road this afternoon. Third is to figure how we block out many of the recommendations for research that we've heard now – some of them more specific than probably they would like to see at the end of the day when we put them all together into a series of bullets. Because, somewhere, we're going to need to prioritize and I really don't want to leave anybody's ideas out. So, the way to prioritize is to blend them together into larger categories of the research that we need. Yes, Dr. Bell.

Dr. Iris Bell

I have a comment that may help with the integration which is, there is within statistical methodology, a multi-variate approach involving causal modeling, linking variable modeling. It seems that in hearing the discussion in the last two days that that would allow us to incorporate many different ideas appropriately so that we can actually see the path from any given factor through a particular construct into symptomatology.

Dr. Barry Wilson, Chair

Are you suggesting another broad category there would be modeling?

Dr. Iris Bell

Yes, sure. But it would take into account all of the information all of these other approaches might be generating.

Dr. Barry Wilson, Chair

Quick, Bob. Do you have a suggestion? We don't do therapy. I don't write prescriptions.

Audience Member

You do, but we haven't broadcast it, Barry. I wonder if that wouldn't be a modality. . .

Dr. Barry Wilson, Chair

Therapy? No. It's not for the pathophysiology and etiology session. We have to contain ourselves.

Audience Member

I'm just thinking for political purposes, you might want to include some language in that area.

Dr. Sheila Newton
Director of Policy, Planning and Evaluation
Office of the Director
National Institute of Environmental Health Sciences
National Institutes of Health
Research Triangle Park, North Carolina

The overall recommendations from all the working groups are going to be pulled together.

Dr. Barry Wilson, Chair

Thank you.

Dr. Peter Spencer

Just a general comment. Among these many interesting suggestions are some for which a lot of thought has been given and a lot of work has been done. Maybe, Mr. Chairman, those panel members who are familiar with some of the issues that have been raised and the work which has either been done or is ongoing, might wish to comment just as a matter of exchange of information. For example, the last speaker spoke of the need for epidemiology. Well, a number of epidemiological studies have been funded, are underway, results have been generated. Information apparently has not been dispersed as widely as it might. That type of comment can apply to many of the, to some, if not many, of the questions which have been raised. And before we proceed down the path of thinking up new ideas, new ways of doing things, perhaps those people who are knowledgeable could comment on what we know already in relationship to the questions which have been raised.

Dr. Barry Wilson, Chair

Okay. I am prepared to adjourn for the moment the public comment session and to have the members of the panel now start to put their druthers in how we can put together our recommendations. Dr. Spencer had suggested that we start by each of us commenting on the bodies of work we know about and, by inference, the data gaps. Would you like to start?

Dr. Peter Spencer

In order to do a thorough job, I would want to look at all the points, and maybe you could scan that down to the beginning.

Dr. Barry Wilson, Chair

Okay. Why don't we reprise what's up there? Dr. Newton, if you could run this down, then we can see those. The ones we have talked about have been handed out to you. There's a list of them, too, of what came up yesterday.

Dr. David Ashley

We've got a lot of points that have been made, a lot of overlapping. Is it possible for us to organize them to some degree so that we can talk about subject groups together? Because they're still pretty disorganized.

Dr. Barry Wilson, Chair

That's what I was trying to see how we get to do in our goldfish bowl. That's why I've adjourned the public session. I'll take the flack for that. Because we've got so much information we've got to put together now. Okay, let's start looking at what the input was, and then taking our own input and looking at them.

Dr. Barry Wilson, Chair

Okay. Let's take it from the top because now we have all this input. So, should I go down them quickly and say them as we're looking, and then maybe . . .

Dr. Peter Spencer

Barry, one other quick suggestion, if I may. We have three charges, do we not? Etiology, pathophysiology, and mechanism. Why not take those one by one – start off with etiology and pick up those which are maybe relevant to etiology, those relevant to . . . just a suggestion.

Dr. Barry Wilson, Chair

They get sorted out there on that board by Bill. Why don't we all look at this and see where the Etiologies are? The genetic susceptibility studies. Is that an etiology? Okay, that's one. Maybe, Sheila, can you star them? That's right. Yes, call that an "E." Put a red "E" on that. The suggestion is to label each one as we go down for whether they're etiology, pathophysiology, and mechanism. Okay? Screening for sensitive physiologies? What's that? "E." Role of cholinesterase is needed for accurate testing. That's a mechanism. You see, that's why I had biomarkers. That's okay. Is that another "E?" "M?" Okay. Mechanisms now becomes biomarkers, too, in a sense. See, the categories will shift. Desensitization as a source of Gulf War illnesses. Mechanisms. Our group says mechanisms. Limbic dysfunction. That's all one thing. The animal model for sensitization. It's in there. All right. Brain, endocrine, immune systems need to be studied. Again, that is mechanisms.

It's not going to work that way. Okay. Well, if we make a false start . . . I come back to my statement that some are at the stage of hypothesis testing, there are others that are biomarkers and maybe there are mechanisms. There's nothing wrong with etiology. Then there are ones where there are real data gaps. Now, how are we going to sort this out without getting into a locked room? Pathophysiology with mechanisms? Okay. We've still got a list here that we have to narrow down. So, why don't we go down and take a look at them now, and then we can go back to the big categories, and this will all fall in line. Because after that, I want us to start thinking what the priorities are. Nobody's suggestion is going to be excluded.

Okay, so we have:

- blood tests for exposure risk assessment,
- predictors of genetic susceptibility,
- mechanisms of delayed pathologies - the delay comes in here very often,
- transgenic animals that over-express markers,
- novel treatment strategies,
- anti-sense DNA,
- examine toxicant induced loss of tolerance in susceptible individuals,
- susceptible people – proposal for the controlled isolated hospital environment,
- evaluate the neuro-degenerative disorders in Gulf War veterans. Now that's come up before. Obviously neuro-degenerative disorders and whether they're tied in or not. Some of us, Dr. Spencer and I, have looked at neuromuscular abnormalities, and we're very careful about what gets diagnosed what.

On to the exposures:

- low level chemical weapon exposures,
- the prospective health assessments of communities - so we may be set for the next one where we need the same kind of work,

- quantitative structure activity relationship modeling to predict chemical toxicity in relevant receptor systems - this is a lot like what Dr. Bell was just saying here.

Dr. Iris Bell

Well, actually, what I'm talking about is across categories, so I'm talking about expanding out genetics and environment into a larger grouping.

Dr. Barry Wilson, Chair

Yes, I understand that. What I'm saying is we have some kind of modeling areas showing up here.

- the proportion of unexplained illnesses,
- segregating separate sets to set out chemical and physical agents, psychological or physical stressors, and determine these cross associations,
- the interactions between environmental pollution and stress - That's come up quite often, specifically the role of sand, fine sand, which is definitely in the Central Valley of California a respiratory problem, silicosis amongst farm workers and farmers,
- check the interactions of Gulf War exposures with stress and exertion, can that amplify the effects of pyridostigmine - It is quite true, pyridostigmine is not the antidote, it is a prophylactic. The antidote that is given is atropine. Can it effect the toxicity and pharmacokinetics?
- toxicological testing on mixtures,
- low level exposure, neurotoxic effects,
- study oil fires,
- other non-chemical exposures - What is EMF? Oh, the electromagnetic field. No one has found very much with EMF in a lot of studies. There's been a lot of money thrown at this by the electrical industry. That doesn't mean that our super weapons may not magnetize my eyes and ears,
- a centralized Gulf War library - that was a marvelous input.

Onward now to today – next we'll summarize:

- the congruence between MCS and porphyrinopathy - I hope the panel are thinking of how we lump these,
- oil fires,
- the relationship between cerebral blood flow and metabolism with brain SPECT imaging and red blood cell morphology is what we're talking about here,
- Do more immunotoxicity testing on Gulf War vets,
- standardize the clinical trial testing,

- get to cellular level,
- investigate sex biases - this has come up, last night too, of more problems in one sex than another,
- oil well fires, again,
- look more carefully at the research that has been done - if you don't know where you've been, you're not going to know where you're going, but you got to renew the commitment to ethical principles. That comes in, a lot last night, this is a quick comment that maybe I shouldn't make, but I sat there for three hours, and that is, for all the veterans that come up and ask that they be made subjects, I can't do that. I don't run that kind of camp. There are studies that can and should be done on humans, and there are studies that can't and shouldn't. That's where our experimental animals come in, our cell alternatives, whatever else we can. So, sometimes, if we're not studying a veteran, it's because we're not going to subject you to any of the kind of things that we first start out with our animals. Okay, onward.
- delete psychiatric research - we're not ready for it yet, that was the recommendation of a psychiatrist.

Dr. Iris Bell

That's a policy issue.

Dr. Barry Wilson, Chair

- funding should go to treatment studies . . .

Dr. Iris Bell

Policy.

Dr. Barry Wilson, Chair

That means none of us here, we can shut up and go home.

Dr. Iris Bell

Recommend it to Congress. Okay, our role is to look at the areas of that go from the individual on down it looks like. Let's go on.

Dr. Barry Wilson, Chair

- look in ICD and change the terminology so it's called "chemical hypersensitivity" - again, a

policy thing.

Dr. Iris Bell

Epidemiology, it's in ICD already.

Dr. Barry Wilson, Chair

- some research on cholinergic activity of the pupil - the eye has been recommended for over 100 years from time to time to use for biomarkers of various disorders. Whole books, whole things have been placed on that. This is very interesting input here.
- look at cellular energetic deficiencies and blocks - none of these are mutually exclusive. We're looking at that hierarchy that I described the other day,
- interactive studies to look at pre-morbid indicators of delayed neurological disorders,
- the red cells,
- the improvement of neurological evaluations with respect to cranial nerves - the olfaction showing very high levels, and vision and audition, too,
- lymphocyte testing, testing for fungus, viruses, for other inputs that are confronting the human system,
- different groups of people that have different disorders - just as a comment, in the history of an area I know a lot about, cell culture. How could we regulate the pH of the cell culture medium until somebody had defined pH and had a pH meter? We face similar problems at many of these levels. If we're trying to fix a particular disorder and calling it "croup," we may have overrun our headlights. But that's what we do research about. So, I'm not bothered about it, but I'm not surprised if we have different groups of people with different disorders.
- depleted uranium - there was enough circumstantial statements made last night to make it clear that needs a hard look on a research level. Please take the microphone. The public discussion is over because nobody has come up, but go ahead.

Audience Member

I work with Dr. Durakovic who was uninvited to this conference.

Dr. Barry Wilson, Chair

I didn't make out the invitation list.

Audience Member

I understand what you're saying, but he is a specialist in depleted uranium, and he's a physician

and in terms of research . . .

Dr. Barry Wilson, Chair

Okay, we've just put this on our research list.

Audience Member
I understand that. He's given me some specific things that . . .

Dr. Barry Wilson, Chair

Not appropriate at this time. You can turn it in, but the fact that we've put it up there . . .

Audience Member

You just want generalities up here? You don't want the specific studies?

Dr. Barry Wilson, Chair

We're trying to get to our recommendations or we'll never get done with our work.

Audience Member

I see. All right then.

Dr. Barry Wilson, Chair

We're on your side. So, why don't you give Dr. Newton your stuff, please, and then chew me out later.

- investigate ALS - the ALS connection has come up several times and I think it needs to be looked into,
- birth defects,
- causative agent detection efforts improved - there's our biomarkers,
- epidemiology to identify and characterize hazards,

Are there any more now? That's it. Okay. Now, we've all gone through it again. Do we see ways of lumping these so we can . . .

Dr. David Ashley

We could look at it from a causative standpoint.

Dr. Iris Bell

We could bring it back to two very broad categories of genetics and environment and their interaction.

Dr. Barry Wilson, Chair

Another way is to look at different levels – bio, cellular, organ, animal, human and population. That may not break out, but it would give us a cut. That breaks it out to the health effects side. You have almost a matrix.

Dr. Iris Bell

It could be a matrix.

Dr. Barry Wilson, Chair

So, what we're talking about now is a matrix. Going across would be the different levels from molecules up to – we need something simple, I don't know, that may bog us down. The audience can listen as we hammer out these recommendations and think about how dumb we are as we do it.

Unidentified

I would suggest that when we have these categories in place, that the audience maybe chooses five things for each person and votes for the ones they like.

Dr. Barry Wilson, Chair

Why don't you let us get some categories. That will be . . .

Unidentified

That will be fine, but I'm suggesting that we have some audience participation in prioritizing.

Dr. Barry Wilson, Chair

That will be happening before we're done. I swear it, okay? But right now, how do you guys want to characterize it? You just think of us as your television screen.

Dr. Claudia Miller

I think Dr. Graveling's idea of exposures and mechanisms and outcomes, I can mentally put things into those categories, and then obviously there's going to have to be this other category for some of the policy issues. But, those categories, you don't want too many. I think those are ones we can fit in, and then if we can't fit something in, we'll try to deal with that again. But I think mostly, that will cover things.

Dr. Barry Wilson, Chair

So, you want exposures, mechanisms, outcomes, and other put down one side. Are you prepared to buy into my stages where you have hypothesis testing, biomarkers, data gaps. Now, they're not quite that, but they show different things we're looking at, and certainly when you're up to hypothesis testing, it's different from when you're trying to get biomarkers to find out exposures and levels, and certainly when you notice a data gap where there's just not enough information and you need new research. Shall we try that?

Dr. Iris Bell

Let me just say that, while this looks absurd, this is actually a small model of what people are actually talking about right now. It does not reflect the specifics, but if you actually look at the organized areas in the middle, as I said, you can start with genetics and environment and you go out to specific factors for each of those. And there are specific hypotheses associated with each of those categories that we can lump under those areas.

The advantage of this kind of modeling is purely and simply that it is possible in large, large sample studies to generate causal models of what involved what, what acted by way of what to come up with a particular result. And there is a statistical way of doing this. There are methodologists expert in doing this. I am not one. I simply have come to appreciate that it can be done, and they draw models like this and then generate them into numbers and they will show you what these relationships are if they have a sufficiently large sample. Given the complexity and given the emphasis that we've had on multi-factorial issues, it seems that this approach is how we're going to end up being how we organize it in the end when we look at relationships. It's too complex obviously to put in an outline form. But, I think we're going to have to do this kind of modeling in the end in order to generate the full picture.

Dr. Barry Wilson, Chair

Eventually, but not within the next couple of days. How do we get from here to recommendations on Tuesday morning.

Dr. Claudia Miller

Let me comment. She has environment there. We've got exposures there. She has symptomatology and we've got outcomes. So, those are really equivalent pretty much. And then, we have mechanisms which is a little more broad and you're taking it as a host factor – genetics.

Dr. Iris Bell

And some of the mechanisms are blending into how the environment is having its effect. So, yes, I mean, that picture would get even larger. But, yes, that would be the kind of thing we were talking about.

Dr. Barry Wilson, Chair

There is something in the middle and it's the kind of diagram where you use circles that overlap, so you have environment circle, you have systemic circle, and that's the overlap. You can put it together. That's for us to understand. I'm really in the mode now of getting us to hammer out recommendations of the areas of research we want. And for that, the best is either a list or a matrix.

Dr. Barbara Sorg

I'd like to see come out of this, whether we do it now or eventually, but I'd like to see a listing, probably it would be under exposures, of DU, petroleum oils, pesticides, protective agents, the prophylactic agents. I've been learning things as I've been sitting here the past two days, and I want to make sure I haven't missed anything, that all those things are listed.

Dr. Barry Wilson, Chair

Can we take this as a test category now? You're saying under exposures, we now would have to decide whether there are markers for finding something or we're ready for hypothesis testing, people know enough, or it's a data gap that's gotta get filled? DU I say goes here. It's a data gap. What was the next now? You had a list.

Dr. Barbara Sorg

Somebody mentioned petroleum oils.

Dr. Barry Wilson, Chair

Are they also here in a data gap?

Dr. Barbara Sorg

Yes.

Dr. Barry Wilson, Chair

There, the oils are in a data gap. So is smoke then for what we're concerned about. And sand. Big time, sand. What under exposures? (In the background: Experimental vaccines). Vaccines are a data gap. What about hypothesis testing?

Dr. Barbara Sorg

There's also the antidotes that were used.

Dr. Barry Wilson, Chair

Yes, but are these all going to be in data gaps? Are those all data gaps? Or are we looking at . . .

Dr. Peter Spencer

I'm deeply troubled by this process.

Dr. Barry Wilson, Chair

That's up in the hypothesis area then? For which ones? You see, if the work is hypothesis driven, then we aren't just trying to scope this out. We have a particular theory we're testing. Peter.

Dr. Peter Spencer

I'm a little troubled by this process because we can all produce our favorite chemical, or drug, or vaccine, or whatever. But, we're not really thinking about this as being driven by a scientific process, I would suggest. We're just throwing these categories out. There is a tried and tested way of approaching a disease that breaks out in the workplace. If you consider Southwest Asia a workplace, if you consider that a disease broke out, the traditional way is to find out when it broke out and where it broke out. That is, one goes after the spatial, temporal distribution using traditional epidemiological methods.

It is quite clear that the illnesses which veterans suffer today, are seen among the civilian

population who did not go to the Gulf. However, it is also abundantly clear that the illnesses are in excess among those who did go to the Gulf. We have that as a solid starting point. However, we don't know whether that excess illness among those who went to the Gulf appeared at a certain spot or a certain time. There are some recent data published that I mentioned yesterday which suggest that there is not a great deal of difference in the proportion of cases of unexplained illness among those who were in the Gulf for different discrete periods of time. Although, interestingly enough, there is a trend for an increase among those who were there for the clean-up period during the period of the oil well fires.

I don't want you to run with that. I just want to present before you that there is a tried and tested scientific method for investigating an outbreak of disease in a workplace. You accept the fact that you may find a number of confounders in that workplace setting. For example, in Columbus, Ohio in the 1970s, there was an outbreak of peripheral neuropathy. Everybody said, "Well, it must be the methyl ethyl ketone, and it might be the methyl isobutyl ketone. It can't be the methyl *n*-butyl ketone because EPA said we must use that because it doesn't pollute the environment." And there are a number of other chemicals there in the workplace. Okay? Careful epidemiological study by the Ohio Group demonstrated that, in fact, the only new chemical that had been introduced into the workplace was methyl *n*-butyl ketone. They demonstrated that there was a site association between the use of methyl *n*-butyl ketone and the workers who got sick. There was a temporal, spatial relationship.

Are we going to say that we are not going to go after the tried and tested method of determining whether there is a spatial, temporal relationship between the excess illness among veterans in the Gulf? Are we just going to throw all of that tried and tested methodology overboard and just say, "Well, we should try methyl ethyl ketone, we should try anthrax, we should try this?" What the Ohio Group showed was that, in fact, the EPA recommended chemical, methyl *n*-butyl ketone was the actual cause of the peripheral neuropathy. That hypothesis which was developed epidemiologically, was then tested in animal studies, and conclusive proof was demonstrated that, in fact, a peripheral neuropathy could be induced in those animals. It was then shown, because of the basis of epidemiological suspicion that bystander chemicals might have been promoting the action of this chemical, methyl *n*-butyl ketone, and that was proven in animal studies. We now know today, as Dr. Abou-Donia will tell you, that methyl ethyl ketone will potentiate the action of methyl *n*-butyl ketone.

But, we arrived at that through careful, detailed, spacial, temporal epidemiological assessment of the illness, using a case definition rigorously developed. And then we developed that in animal studies. So, I put that forward to say, be careful before just saying we've got to study everything. Because there might be a scientific method by which we can pin down the more important actions.

Dr. Barry Wilson, Chair

Thank you Peter. I'm sorry the discussion is causing the audience discomfort, but . . .

Audience Member

No, I was just responding. How about the subgroup that never made it to the Gulf and got the shots that are truly sick? I'm just addressing what he said. That's the group that should be studied.

Dr. Barry Wilson, Chair

Thank you. There's another way of looking at it and I'll get to you soon.

Dr. Claudia Miller

Just a comment. It's a very logical way of, I'm just commenting on this . . .

Dr. Barry Wilson, Chair

Well, let me just try this one. There is another paradigm, ties in with what Dr. Spencer was saying, and that is the way that, although we malign it a lot, the EPA goes about risk assessments. First you have hazard evaluation. Then you characterize it. Then you end up by determining risk. But, if you think of the risk, getting down to the causation here, it's exactly the approach that we're talking about here. We have not sufficiently studied all the hazards – the spatial, temporal situation. We have not characterized those risks. To a toxicologist, that means something simple that's profoundly difficult – dose response. We don't have that. But that's where these categories all start fitting in.

There are the four steps for doing the risk assessment, the risk characterization - risk assessment, hazard identification, dose response, and exposure characterization. So, we have exactly the kind of design that Peter is talking about here, but taking out of the context of disease and brought into environmental problems here. Where we have environment and organisms interacting together, and we have people that are sick or brought in things that could now be exacerbated by the situation. So now, we could approach this by looking at what kinds of research have been outlined here to find out the hazards, to characterize, see what the exposures could have been, characterize the risks. What this avoids though, is this is all set up for epidemiology and for numbers, and it avoids the mechanisms that we have to get to as part of our session, and to understand. But, I think that we are getting close to it.

Dr. Claudia Miller

One of the difficulties with Gulf, of course, you had so many different exposures. However, when

you take careful histories on people, you will find individuals like the woman who just spoke, where they were not in the Gulf and there was a specific thing that occurred. They are personally attributing onset to that. I've dealt with Gulf veterans who came back and have been well, and then two years later they moved into a brand new earth home, very tightly sealed, high levels of volatile organics, new carpet twice, and got sick in that home as did his son. Another veteran came back and took a job as an exterminator and got sick when he was working with organophosphates in his job as an exterminator. So, as I've seen these, close to 100 vets now, and done these careful exposures histories, "When did your symptoms begin? What exposures occurred?" And looked for the temporal, cohesiveness between onset of illness and an exposure, you find some very different patterns. Now, if this is true, if organophosphates could cause something that looks just like this, you will have, and this is what we're saying, Gulf vets now who are saying they're sick from the Gulf War because they went to the Gulf War, but was it the Gulf War? Did the Gulf War help enhance it? Is it something separate from the Gulf War and now organophosphates can cause it as well?

So, as a clinician, I don't see any substitute for getting these close temporal kinds of relationships figured out *individually*. This is terribly labor intensive. But to identify people where, another vet who, I'll give you a couple more examples, had onset of illness when Saudi trucks came through spraying pesticides in the Gulf. He had two episodes. Both times right after the trucks came through. And now he's chemically sensitive. Okay? Another veteran who was over there and took, he was a Colonel, and took pyridostigmine bromide, developed projectile vomiting. Clearly the onset of illness was at the time because he started taking that drug in August before the war ever started. Why he was doing it was another issue. But there are these people that have really clear onsets, and then there are other veterans who say, "I don't know. I suspect it might have been this." But, they were exposed to lots of stuff. But, to take those cases where you do have a much clearer temporal link, and they are very good historians in these cases.

Dr. Peter Spencer

Well, they might be valuable, I agree. But, with respect, Claudia, one has to note that among the studies collecting self-reported data on exposures, these are fraught with error, both from studies that have been conducted prior to the Gulf War veterans illnesses and during these studies. Our own data, for example, remarkable demonstrates that, of those people who were there exclusively for Desert Shield, that a quarter of veterans report that they believe that they were exposed to chemical warfare agents. And not even the DoD worst critics would suggest that chemical warfare agents were present during the Desert Shield era.

Dr. Claudia Miller

That's right, and I wouldn't include those in this because I think it is very nebulous. But there are some very clear ones. You've got medical records on vaccinations and onset of illness, and

you've medical records on this guy who had the exposure to the pesticides.

Dr. Peter Spencer

Agreed. I think both approaches are valued.

Dr. Barry Wilson, Chair

One at a time guys. Dr. Peckerman has something to add. We've got 15 minutes and I'd like us to come out with a plan.

Dr. Arnold Peckerman

I would just like to suggest something that may simplify and streamline the work we're trying to do. This has come from our own experience. There are issues related to illness precipitators – something things that cause illness in the first place. A second set of issues relate to what is causing symptoms, what's maintaining illness now. They're not necessarily the same. Both of these are important. If we can keep those separate, we may not be very effective of doing either.

Audience Member

I'd like to just say one thing. One sentence. Designer adjuvants have delayed cell-type hypersensitivity. So, when you get a shot, you can have a reaction later on – months, years.

Dr. Barry Wilson, Chair

Ma'am, I'm going to shut the microphones off. So, what did he say?

Dr. Arnold Peckerman

To concentrate our effort in two separate areas, one of which illness, precipitants of illness, what originally caused the illness and what causes the symptoms now. The mechanisms of symptoms. Maintenance of symptoms presently in the veterans. It's very unlikely that what ever cause illness originally is still present in the environment.

Dr. Barry Wilson, Chair

Maybe we should add something to this. I would still suggest that we separate this out into what's ready for hypothesis testing and what are data gaps. Okay? I think that should be there, too.

COL Andras L. Korenyi-Both

If I may add to the confusion, how do I believe that our charging agency, the CDC, charged us to investigate the chemical hazards among the Persian Gulf veterans? Persian Gulf Veterans are 700,000 men and women deployed. They were exposed to certain chemical material. Certainly, there are adjuvants, and if you would be kind enough to flip back two slides, you already started with and covered the DU, smoke, seasonal disease, no seasonal infections, atmospheric pollutions, depleted uranium, chemical agent resistant coating, pesticides, rodenticides, adverse reaction to immunization, pyridostigmine, airborne, calcium content of the fine Saudi sand, biological or chemical warfare agents – which should be our main course today.

Dr. Barry Wilson, Chair

Excuse me. I don't understand. Is this a list for us to investigate? We have a very long list already, Colonel.

COL Andras L. Korenyi-Both

Yes. What we need is here, sir, to have some kind of red string to adhere and to try to put this very useful input into some kind of workable form. I believe that our charging agency already gave to us – the agency is requesting answers for two questions. A central question - what are the most plausible etiological hypotheses? And this is question two - diagnosed disease, unexplained multiple symptoms and illnesses. Associated questions were five questions.

Dr. Barry Wilson, Chair

Yes, and I started with that.

COL Andras L. Korenyi-Both

So, I think that that's what we're supposed to do. This is just a suggestion from me.

Dr. Barry Wilson, Chair

Now wait a minute. I hope we haven't departed from that. What we're trying to do is block them out. That's why I've kept saying why don't we look at ones that are ready for testing hypotheses, for those in which there are data gaps. Now, Dr. Spencer has said that this whole approach should be taken from the idea of an illness model. I said maybe we could use a risk model to sort out that laundry list. The laundry list is worthless when it comes down to research. We can't come through with the recommendation that's going to look like that. We're blocking them out. So, the other suggestion of Dr. Peckerman is to have an illness and causality, and a

mechanism and symptoms. And I added to it the environment and exposures. Now, I don't know which goes best. We're coming to the end now. We will regroup at 3 o'clock, but I would still like to see if you'd like to keep, sort out, the research areas into hypothesis, data gaps, and think of whether more needs to be done to establish the environment. That almost is like Peter is saying is: What happened out there? And then to see what areas can be done.

What I don't want, and what I see happening here, is all of us are experts in something. We bring our expertise to this Gulf War problem, and then we inadvertently end up asking the Gulf War problem to support the discipline research we think is important. We don't want that. We want, like the Colonel said, we are subordinate to what happened to Gulf War veterans. But I must add, to what happens in the future to the next Gulf War veterans. We've got to get a handle on that.

COL Andras L. Korenyi-Both

Yes, and let me comment on it. That will finish what I started with. I give you a laundry list and you became tired, you know, even to write it down. For good reason. That was my aim to do it, I entrapped you, I have to tell you. Because all of these are involving subsets of the 700,000 men and women that we deployed. It's not for everybody. Out of 700,000, approximately 100,000 claim to be sick. What we need to look for, a common denominator, which would set all of the subsets into under one umbrella. If you would like to call it "Persian Gulf syndrome," please call it. But I have my comments. I don't believe that that's true. Thank you.

Dr. Barry Wilson, Chair

Okay. Dr. Soreq, who hasn't said anything.

Dr. Hermonia Soreq

Well, I was listening here and there seemed to be two suggestions as to the event that initiated the disease. One is Dr. Spencer's suggestion that says there should be a correlation, that is, it should have started some time, and that could give us a clue. The other is Dr. Miller's suggestion that says a little bit like the cancer theory of two events. There may have been two events. So, what we need to do is perhaps to ask to check the hypothesis: Was it a single event or more than a single event? That could link the two theories.

Dr. Barry Wilson, Chair

That's certainly something we can ask for, yes.

Dr. Iris Bell

Just getting back to the mechanism, and at least two other panel members have talked about the issue of temporal association. I mean, if we're going to prioritize possible mechanisms, we have to be looking for things that could cause a delay between the time the insult occurred and a symptom appears, or the disease is diagnosed, or whatever outcome we're talking about. And that way, we can differentiate mechanisms that can only cause short-term effects. There's no point in looking at those unless they have implications for delayed effects.

Dr. Claudia Miller

Right there we can rule out half of the toxicological mechanisms because you wouldn't expect people to be sick seven years later. That's classical toxicology.

Dr. Barry Wilson, Chair

I put in earlier, remember, in one of my first introductory list, that delayed is a very important aspect. And the research and study of delays.

Dr. Peter Spencer

Very briefly, I mean, Claudia's comment is noted, but it should not go unchallenged at some point.

Dr. Claudia Miller

I said *half* of toxicological mechanisms. I didn't say *all* of them.

Dr. Barry Wilson, Chair

What we have has truly gotten down to business in trying to hammer out a matrix of being able to judge the research. I don't want any of us to think that we can't come up with a neat bunch of research that ought to be done. I know we all can here. We're trying to fit it into a palatable package, and we're going to have to continue that at 3:00. But, oh, you had your hand up. Excuse me.

Dr. Deborah Norris

I did. Since we keep coming back to what Dr. Spencer suggested. I would like to address the concept that you mentioned with peripheral neuropathy. In this situation, I have heard from the audience, repeatedly, the suggestion that there is more than one illness and more than one mechanism. I think what the Colonel was alluding to is that there may be many things going on here which does complicate the situation. It's probably why we're having so much trouble.

Dr. Peter Spencer

I wouldn't disagree. But what you just said is a belief system and not necessarily a scientific fact. What many researchers have adopted, and what veterans have called for, and others, is that there be a rigorous definition of the case, a case definition for unexplained illness. Those case definitions have been developed, by the way. They are available, and traditionally one would use that case definition then to explore caseness and lack of.

Dr. Deborah Norris

The same sort of thing happened with schizophrenia which used to also cover ADD, ADHD. We've found out that these are separate entities.

Dr. Peter Spencer

Of course you refine it later. But, you've got to start somewhere.

Dr. Deborah Norris

But, that would stop us in our tracks to try and do that right now.

Dr. Peter Spencer

Well, with respect, I think you've got to start out of some point. Clearly, it would be a crude definition to be refined later. But, to start off with the belief that there are several different illnesses may not be scientifically valid.

Dr. Barry Wilson, Chair

Okay. That's something we may want to decide, or see how to decide right now before we close. Are we going to continue at 3:00 to call for experiments that try to define, give a case definition to a Gulf War illness, or are we going to say that so far as we know now, we must proceed prudently on thinking that there is more than one situation that may be involved, and that we're prepared to fund studies in different areas? Which way do you want to go? We gotta do that right now.

Audience Member

I was told by Bob Newman a year ago that case definition research is proceeding. So, I thought that that should be about finished by now, Bob Newman of Shay's committee.

Dr. Barry Wilson, Chair

Please leave us to grapple.

Dr. Claudia Miller

Certainly case definitions have a lot of value for epi studies. You can also take an exposure driven approach like with the people around Khamisiyah who, perhaps, were exposed to nerve agent and try to look at compared groups – people that were closer and further – and see what outcomes evolved from that, rather than say there's a rigorous case here. One of the concerns I have is when you're dealing with something like this, you know, people may be exposed to pesticides and maybe people exposed to, you know, a variety of other things (solvents, fuels) if they share in common, let's say a general mechanism, of losing tolerance, there's no applicable case definition that would embody all of the symptoms that may come out down the line, and all of the exposures that may have been causative.

Dr. Barry Wilson, Chair

Our problem is I don't know if we know how to call for research to get a case definition. I have to stand up tomorrow and I need some points that are going on a screen instead of into my cells.

Dr. Claudia Miller

And there's ongoing research right now to try to formulate a case definition. I mean, there are centers starting to do this. New Jersey is one.

Dr. Barry Wilson, Chair

My own personal feeling is I want to see what's up for testing hypotheses, what isn't, and then to deal with these very matter that Spencer and we've been talking about for a while. But, I'm trying to see how that converts into research goals. I think we're going to have to quit now, because I'm supposed to meet with the other chairs to discuss our progress.

Let me thank the audience. I know I've been rude. I'm sorry. You can understand why.

The session was adjourned.

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Day 2 – Monday, March 1, 1999 - Afternoon Session

Dr. Barry Wilson, Chair

This is what I started with, and this is what I would show first saying that our charge was to develop recommendations for future research addressing Gulf War veterans. And as was pointed out to me by the panel here, they've already listed some things here. We were charged to deal with chemical exposures, illnesses, synergistic effects of chemicals, subclinical effects, susceptibilities, biomarkers of susceptibility and methods for determining mechanisms. The criteria, I had said early here was that the best science would be the driver – testable hypotheses, relevance to veterans, addressing data gaps, avoiding undue duplication, and for the sake of what we will be presenting tomorrow, it includes, someplace in it, everything all of us have said today.

Good science, but it's got to be short and sweet, and for this sake of this panel and all other investigators that came up, it does not have sandbagging. Our own projects may be identifiable to ourselves, but are not identifiable in what I'm presenting. If we sandbag, we lose credibility, and you can't just say, "I came here to show you my good stuff." So, it's an umbrella. As to whether it's a leaky umbrella or not, we still have some time to work on this. But it's a draft and, all joking aside, it's a very important draft, because we've tried. Sheila's done a marvelous job, and Dr. Abou-Donia, in helping to pull together the disparate things we were all saying. So, I'm going to present that now on the overheads and speak to it. Just imagine, we have only 10 minutes or so to present something tomorrow, it's only 10 or 15 minutes. So we can't, all the things that burdened us are now starting to go away. What you're looking for are flaws. Like I said, no sandbagging. Our favorite things have got to fit under an umbrella.

This is divided up into about 5 categories, and they are bullets, so we can be able to tell the folks quickly.

Number one is *Environmental Exposures and Time Course*. And here are some examples. Time course is a point that was made here. You'll each see something you had said about:

- depleted uranium,
- drugs/vaccines,
- nerve agents,
- lead,
- insecticides,
- repellants,
- petroleum,
- oil fires,
- carbon monoxide,
- sand,

- heat exertion,
- other stressors, and
- infections.

I inserted the "or evaluation of existing research" because there's been a lot of work done on this. But, Dr. Spencer and others have made the points that there is a time course in this and things that have to be sorted out. So this is studies of those environmental exposures.

Number two, *Studies Geared to the Human*. The vets kept saying, "Study me. Treat me. Do it." Okay, we've tried to think of what human studies would be the next step, or looking over what's been done, what's needed:

- analysis of deployment cohorts and how it ties in - is exactly what I think Spencer and others were saying,
- neurological, central nervous system, neurological, and aging studies - the delay keeps being a theme here, exposure once, things happen later down the road,
- immunological studies - I've learned at this meeting and learned from the researchers, some of the investigators here, how important the immunology has moved beyond that sort of welt on your skin for looking at this, to really getting some understanding of what's happening, so immunological studies),
- pulmonary and respiratory - where does that sand go?
- the hematopoietic systems studies - not always exactly what somebody has said they wanted, but it's put in here, that's an umbrella,
- dermal and GI studies - somebody turned in that. I think there's an organ system that ties in,
- genetic screening for known risk factors,
- birth defects and reproductive toxicity - even though we said there's nothing to it, when we approve a drug with FIFRA guidelines for the EPA, you have a 2-generation rat study. I haven't seen any 2-generation rat studies from the Gulf War yet,
- chemical sensitivity - it's a general category, it's not sandbagging, mechanisms of this,
- gender effects

Next are *Animal Studies:*

- synergistic effects of exposures,
- subclinical effects of exposures,
- low-level chronic,
- multi-generational studies,

- gene expression,
- delayed expression of environmental insults.

These are just examples of the kind of animal research that has come out of all of the discussions here, all the things we need without specifying. Remember, we are not going to write the RFA here. We're just presenting these kinds of bullets and trying to tell them that these areas are important.

Then, they've asked for development of biomarkers, remember? So, here's *Biomarkers of Exposure and Effect*. A biomarker is an early warning sign for those of you in the audience that might be saying, "What in the world are they talking about?" Okay, what we're talking about is something that will tell you before you've got it:

- susceptibility to chemical sensitivity,
- biomarkers of stress,
- biomarkers for chemical agent exposures - there may be others, but biomarker work.

They call for *New Methodologies* - some of this fits in here:

- The chemical molecular analysis approach to molecular Interactions,
- Dr. Bell, I tried to phrase in a multi-factoral statistical models - some examples are gene and environmental interactions and confounders that may be showing up in the work that we're doing,
- transgenics - knock-out genes for studies of genetic susceptibility), and
- something we haven't talked about, alternatives to animal systems - the role that can be played by highly developed cell and tissue cultures. I teach a class that has 24 students in it right now and each one of them is doing their own special projects that was devised for themselves. This is a logical approach.

And then the *Special Needs*:

- centralized Gulf War research library and data repository - Ms. Wilson's Chemical Injury Information Network has 30,000 documents already to deposit.

So, that's the bullets. That's our summary of what was a rather raucous morning. Let's see if we can put it together, discuss it further. It's now on the table, open for discussion. My feeling is that if all else fails, I could go with that tomorrow. I'm not looking for audience discussion now. We're back to the old rules. It's at the end of the time. Thank you. Dr. Soreq.

Dr. Hermona Soreq

First, I'm amazed how you can up with such an organized list out of the morning discussion, so congratulations. Two types of new technologies that I find missing is first imaging techniques that are non-invasive and very important for evaluation of a lot of symptoms. And the next one is

anti-sense technology which is very different from knock-out.

Dr. Barry Wilson, Chair

This was not meant to be exclusive. It was our best shot, and I agree that both of those were mentioned and that both of them are important. And I guess that Dr. Newton is writing those down now. If I take notes I won't be able to keep track. That is something that can easily be added in there. What I don't want is our list to become a bunch of separate laundry lists. This is enough bullets, and that's just fine. Because with new technology, that's important, I agree. So, I think that ought to be in.

Dr. Peter Spencer

A point of information, if I may. This remarkable consensus list we are on the way to developing, was this developed out of the discussion this morning or the discussion this morning plus the written submissions?

Dr. Barry Wilson, Chair

Yes, this was both. But, something may have not gotten in right. So . . .

Dr. Peter Spencer

I may have missed on. I wonder if I could just share this with the group? This nation has embarked on the destruction of its chemical weapons stockpile. It has begun in the Pacific. It is proceeding at Tooele, and is about to begin at another 5 or 6 sites around the United States where we harbor huge concentrations of sarin and mustard gas, principally. These efforts will be completed in a highly ordered manner, a highly controlled manner by an incineration process which has been proven to be reliable as far as we know. But, nevertheless, it will result in the emission of small amounts, very small amounts, of sarin and mustard gas into the atmosphere. Very small amounts of this material will reach civilian populations.

Now, to bring this into focus a little bit, I can show you just up the road from where I work, a population of 25,000 people who live within 3 miles of this activity that will take place at the Umatilla chemical depot. If all goes well, nothing is expected to happen and nothing should go awry. That's a tautology. I'm sorry. What I mean by that is that no illness is anticipated as a result of this activity. From the research point of view, it represents an extraordinary opportunity and a unique opportunity that will never be repeated – we hope – to determine the potential adverse health effects, prospectively, of exposure to extraordinary low levels of chemical warfare agents which will be with us for a very long time. Or in the absence of actual measurable exposure, the perception of exposure to chemical warfare agents.

While this does not directly relate to Gulf War unexplained illnesses, I believe that it represents an opportunity for us to learn from an activity which will never be repeated again. I would hope that the panel and the audience would give some consideration to this possibility.

Dr. Barry Wilson, Chair

First off, Dr. Spencer knows I volunteered on every occasion to work with this project. Secondly, I do beg his pardon that a category was left out. The charge was the Gulf War, and my 3 hours last night maybe sensitized me very much to the veterans of today. I think we need to think about the veterans of tomorrow and the civilians of tomorrow facing – who knows? So, I would propose we put in, as a number 7, or maybe as a number 6 and let special needs be number 7, future related problems. And the first one is destruction of chemical warfare agents. Now, there may be a part B in there too. There must be problems that relate to the chemical warfare, but try to think of it in an umbrella sense. Please don't sandbag. Each one of us has our favorite experimental problem, where we know what's wrong. We're trying for these categories, and that one, certainly, the destruction of the chemical warfare agents, is an opportunity for some of us neurotoxicologists. And I may be the only one here who also, without benefit of a license, is an ecotoxicologist. I think some of the early warning signs for us are what's out there in the environment. So, I chime in on that. I would add that on to that, and I'm sorry we forgot it. If the list gets too long, we're going to have to chop it back. But this was a real omission. This is up on the screen now, so we can think about it. But what we need now is, truly, from now on in, consensus. Let's finish this off so we can have an evening to think about it, and then tomorrow, really finalize it.

There's one other thing I forgot. We are pretty well charged with having to think about short-term and long-term. The definition of short- and long-term is 3 years and 5 years, and I don't want to quibble and argue about it. So, I don't know what's short and what's long, but we need to think about that, too. What I was doing, with the help of Sheila, is an artful trick to get something I know we can go with, to represent something in here that everybody has said. And now, we can start to clean it up. But, if we throw it away, I don't know what we're going to do for an encore. So, I don't what's short- and long-term is. That's on the table.

Dr. Deborah Norris

Just a quick question because I don't know the answer. I see chemical warfare agents often described along with biological warfare agents, and I know that there are some problems with those still existing. Should that be included?

Dr. Barry Wilson, Chair

Well, I'm asking. There are people that will start hollering that there were biological warfare

agents used. We were instructed about chemical here. But, then again, I . . .

COL Andras Korenyi-Both

We can include both because there are certain evidences that Iraq deliberately tried to use biological agents, aflatoxin, 19-20 January in Al Jubail.

Dr. Barry Wilson, Chair

Sheila, go back up to the exposure part.

Dr. Peter Spencer

The other part is that it's really an artificial division to some extent in that something like trichophosine is a chemical product of a biological material.

COL Andras Korenyi-Both
Aflatoxin is a a living agent.

Dr. Peter Spencer

Aflatoxin then. Let me choose that. It's a chemical product with biological . . .

Dr. Barry Wilson, Chair

Do you want to insert nerve and biological agents, or put it in under infections?

COL Andras Korenyi-Both

It's not infection anymore. It's a biological agent.

Dr. Barry Wilson, Chair

I know that. Do we want to say this needs looking into more? Do we all agree? Okay. I'm going for consensus. We don't need to go through a lot of justifications if we all agree. Do we believe that biological agents go in? Okay. Biological agents go in before infection then.

Dr. Claudia Miller

Under this last category, added special needs, these are really exposure driven kinds of studies related to exposures the veterans have had, opportunities for research which might not just

include the chemical warfare agents, but also, pesticide exposures since that was a huge part of what was available and very well documented in the Gulf, and oil well fires. I mean, there are other agents, and, I would suggest when we say things like special opportunities – exposure driven research such as. I think we need to have a "such as" there just to keep it clear that we're not being exclusive in our lists.

Dr. Barry Wilson, Chair

Sheila, come down to the special needs category, this might be a very good idea.

Dr. Claudia Miller

I'm sorry it was future Gulf War problems. Related and exposure driven studies - that should be the category.

Dr. Barry Wilson, Chair

Oh, you want a separate category?

Dr. Claudia Miller

No, that would be Number 6.

Dr. Barry Wilson, Chair

Oh, 6, instead of "future" is "related exposure driven studies." Okay.

Dr. Claudia Miller

Then I would add to it pesticides and oil well fires as examples of things that would be good exposure groups, if you could study them cleanly, that might give you information, or following exterminators prospectively.

Dr. Barry Wilson, Chair

Yes, that may be a red flag. I study agricultural workers. There's chemical warfare in the farms and fields of these countries going on every day, and when I say it, it falls very flat. So, I don't want to put political spins on things I know I've been burned at. Don't be surprised if that doesn't make it through. But, if you want it in . . .

Dr. Claudia Miller

No, no, no. That's all right, I think pesticide exposures is fine. Keep it general. The other point, I don't see on there where we've kept this concept of having people evaluated in an environmentally controlled facility and this toxicant induced loss of tolerance question. And that really has two aspects, one is the initiation and the other is the triggering of symptoms and using an environmental medical unit to evaluate – somewhere that got lost. It's a mechanism.

Unidentified

Is this under library?

Dr. Barry Wilson, Chair

No, no, that's not it. It got lost in the sandbag, ma'am.

Dr. Claudia Miller

I know, it happens. We could put it back.

Dr. Barry Wilson, Chair

No, maybe we don't. You're speaking for your own facility.

Dr. Claudia Miller

No, I'm not. I'm talking for a general mechanism that needs to be tested.

Dr. Barry Wilson, Chair

Okay. Put it in a general way. I might as well make enemies of the panel as well as the audience.

Dr. Claudia Miller

This is actually terminology that's been used well beyond this particular meeting. This would be testing the question whether chemical exposures, certain chemical exposures could cause loss of tolerance resulting in, you know, multiple intolerances and people having adverse responses to it.

Audience Member

Why isn't that under chemical sensitivity?

Dr. Claudia Miller

Perhaps it should be, as a mechanism. The use of a controlled exposure facility is very different from just saying, "Let's talk about chemical sensitivity mechanisms." It's a diagnostic, treatment, and a research tool.

Dr. Barry Wilson, Chair

You want a special facility, for us to propose that a special facility be built? That is what you are asking for?

Dr. Claudia Miller

So that you can study people in the absence of background exposure noise. You need to have it. Somebody needs to have it.

Dr. Barry Wilson, Chair

Well, you put us in kind of a hard place when you're the one who wants the facility. Go on down. [Simultaneous conversation from the audience]. Do you want me to clear the room, too? I can make all kinds of enemies. Everybody will go and I will be left with my own idea.

Dr. Peter Spencer

I was actually arguing for 7 sites in the continental United States. That's certainly not my research project. It's the Department of Defense's research project.

Dr. Barry Wilson, Chair

Okay. I will ask the panel if we want to. I tried to avoid very much giving the impression of sandbagging, and I think that it's very important that we do so, that we behave without fear or favor, love or hate.

Audience Member

The flip side of chemical sensitivity is resistance. Once you have an understanding of baseline, you can begin to understand [distant from microphone in the audience, and then simultaneous discussion erupts].

Dr. Barry Wilson, Chair

Maybe it's not phrased right. Go all the way down to the bottom.

Dr. Claudia Miller

Intolerance.

Dr. Barry Wilson, Chair

Be tolerant with me. Go all the way down, all the way to 7 or 5 to where we do our special things. I think what we're talking about ought to be under special needs for a special facility for, now how do you want to . . .

Dr. Claudia Miller

Specialized facility for reducing background chemical noise so you can test effects of low level exposures in humans.

Dr. Iris Bell

Comprehensive, the word "comprehensive" as opposed to "specific."

Dr. Barry Wilson, Chair

Let's see what the committee thinks about it.

Dr. Deborah Norris

Claudia is in an awkward position because this is along her line, but she's valuable for bringing it up because I have heard many other people suggest this, and I've heard these people say they were representing other veterans' interests in having this type thing. So, I would encourage it and I have nothing to do with it.

Dr. Barry Wilson, Chair

Okay then. Do we call it special facility for sensitivity research, chemical sensitivity research?

Dr. Claudia Miller

The term that's been used is either an "environmentally controlled unit" or and "environmental medical unit," otherwise, people think you're talking about an exposure chamber, and if you don't get people to a clean baseline, the theory is you don't get accurate testing.

Dr. Barry Wilson, Chair

The more specific that you get it here, the more controversial it gets.

Dr. Claudia Miller

So, an environmentally controlled hospital unit, or environmentally controlled medical unit.

Audience Member

What does that have to do with anything? That's illogical. If you say you want to study sensitivities, then that will come up in methodology . . .

Dr. Barry Wilson, Chair

I have asked and I mean it, please audience, the time will come in later. We're going to fall apart again, and then I'm just going to take in what we've got now. So, panel be warned. Audience be warned.

Dr. Iris Bell

Just to follow up on that, just separate from the issue of it being Claudia's thing, all of us in the field of MCS, would support someone having it, even multiple sites having one. So, I certainly wouldn't object to that being there.

Dr. Barry Wilson, Chair

Okay, forgetting the name, do we all support some kind of special facility? Then we'll nail down the name. Are we all agreed? Okay.

Dr. Iris Bell

But, I have some other comments. There's some other additions.

Dr. Barry Wilson, Chair

Oh, no. First, we don't have a name for this that's satisfactory and that the audience and ourselves can see what we want.

Dr. Claudia Miller

If you say environmentally controlled medical unit, that takes in all the terms various people have used for it.

Dr. Barry Wilson, Chair

Okay, let's say an environmentally controlled medical unit can be used for many, many other things. This needs to be done to assign variables, and reduce noise level? That would be appreciated by most scientists.

Dr. Claudia Miller

I don't care, but it needs to be in there.

Dr. Barry Wilson, Chair

No sandbagging.

Dr. Iris Bell

I would like to make a small addition. We left CARC paint out.

Dr. Peter Spencer

We also missed mustard agents.

Dr. Barry Wilson, Chair

Nerve and mustard agents. Okay.

COL Andras Korenyi-Both

Nerve and blister agents, and sand – to study sand in general.

Dr. Hermonia Soreq

Well, I may be blamed for sandbagging, but exposures gathered in different countries should be compared.

Dr. Barry Wilson, Chair

That could be in the preamble.

Dr. Claudia Miller

The sarin experience in the Japan subway may be relevant to Gulf War illnesses.

Dr. Barry Wilson, Chair

We're charged with Gulf War. Looking for further information . . .

Dr. Peter Spencer

Tokyo might be valuable information. That might be something for the library.

Dr. Barry Wilson, Chair

Thank you very much. We should not detract from the focus of veterans.

Dr. Arnold Peckerman

I would like to add one more item. It's a co-factor. Included in individual circumstances was war stress. Stress as an interactive factor as moderating the effects of psychosocial.

Dr. Barry Wilson, Chair

This was the chemical and environmental part. We assumed that was dealt with in the human context.

Dr. Deborah Norris

Is the point that these are all stresses? Would you like to call it stress (i.e., heat)?

Dr. Iris Bell

No. It's very dangerous to call everything stress.

Dr. Barbara Sorg

I would suggest leaving that as global as you can, leaving it as just the way it is. At the top you have individual and interactive, implying that any of A through N, any one or more of those could be interactive, and I think that's probably that's best left the way it is.

Dr. Claudia Miller

Keep it interactive rather than the primary focus.

Dr. Barbara Sorg

I just have one tiny addition if you didn't have it already. Under the animals section, you may have this already, but because you have gender differences or gender effects in humans, you could put sex differences in animals if everyone's agreeable to that.

Dr. Barry Wilson, Chair

Yeah, obviously it was left out. Excuse me. Of course.

Col. Andras L. Korenyi–Both

I want to speak about that. I'm not sure why we should use gender effects under chemical sensitivity exclusively. I think gender effects can be a factor in any of those.

Dr. Barry Wilson, Chair

So, you'd rather see it as a K.

COL Andras L. Korenyi-Both

Right, as an individual focus of research.

Dr. Barry Wilson, Chair

I'm easy. Gender effects goes up, and you want to get rid of mechanisms, too. Just get rid of Number 1 and 2 and call it, and go to K, and then have gender effects as its own category. And we're assuming that we have moved to hypothesis driven mechanisms studies.

Dr. Claudia Miller

Mr. Chairman, are we going to try to prioritize, or is that part of our mission? Prioritizing in terms of what areas.

Dr. Barry Wilson, Chair

No. The prioritizing was not part of our mission, and I, after this morning, I became very much a consensus advocate instead of prioritizing. It would be hard to move me off of that right now. I see the end of the line there. Don't ruin it.

Dr. Deborah Norris

On 1(f), may I recommend pesticide in lieu of insecticide?

Dr. Barry Wilson, Chair

Dr. Abou-Donia should speak to why he wants insecticide there.

Dr. Mohamed Abou-Donia

Pesticides, there were two categories, insecticides and insect repellants. These are the only pesticides that were there. So, since we have the repellants as a category by itself, we had, the others would be insecticides. If we used pesticides, it would be we lump both of them together.

Dr. Deborah Norris

So, we're not including anything, there was no use of fungicides or rodenticides?

Dr. Mohamed Abou-Donia

I'm not aware of that. Were there rodenticides?

Unidentified

They were shipped.

Dr. Mohamed Abou-Donia

Then, if this was the case, we should have it pesticides.

COL Andras Korenyi-Both

Can we use both expressions – pesticides and insecticides.

Dr. Barry Wilson, Chair

We may confuse people.

Dr. Mohamed Abou-Donia

No, pesticides includes insecticides. It's a more general term.

Dr. Barry Wilson, Chair

Okay, so we go back to pesticides.

Dr. Mohamed Abou-Donia

So, if you want to use pesticides, then we could use as well as, we can use pesticides, then we have the names, well that's fine. But, do you want to include rodenticides?

Dr. Deborah Norris

If they were used, I would like to include it.

Dr. Barry Wilson, Chair

Well, we don't know.

Dr. Deborah Norris

If we don't know, then perhaps we should be inclusive rather than exclusive.

Dr. Barry Wilson, Chair

Well, that's what we are. These were specific issues of Lindane, of the organophosphates, and they should remain in. This was specific veterans' input.

Dr. Mohamed Abou-Donia

They should be included. Some uniforms were impregnated with permethrin, so, this should be included.

Dr. Barry Wilson, Chair

So, we need the pyrethroids, the Lindane and the OPs. So, why don't we put that in there. If there are rodenticides, I don't know whether we ought to be concerned about it. Your time will come, guys, okay? There's gonna be a comment period. Right now, I want to see how we're coming at getting this finally hammered out before you hammer me.

Dr. Satu Somani

Can you give us some examples of the drugs there?

Dr. Mohamed Abou-Donia

Pyridostigmine bromide.

Dr. Barry Wilson, Chair

If you want drugs, e.g., pyridostigmine bromide, put it there. That could be good enough. Well, you put that in after drugs, and let the vaccines stick out on their own. It's drugs, Pyridostigmine Bromide, and vaccines. [Distant comment from the audience] Later, please, ma'am.

Dr. Satu Somani

I know this may be irrelevant, but 65% of the veterans used alcohol, and we never discuss anything in the whole meeting of the interaction of the alcohol and the drugs. I don't know if this is important or not.

Dr. Barry Wilson, Chair

This is not a wish list. This is what we stand behind for long research. I didn't mean it the way it came out. I mean, we could list a whole long amount of chemicals. Do we wish to include alcohol is something for active research to be done on them. Do we see that as a very real factor in the Gulf War? That's the question. I haven't heard that at all raised until now. No takers. Do you want alcohol?

Dr. Arnold Peckerman

This would be related to human studies, oh yeah, it is there. I'd say there is one major, major physiological system missing for research – the cardiovascular system. Respiratory is probably very important because of whatever chemicals that come through air. But, it's all distributed through the blood flow. Excluding cardiovascular system, individual differences and problems can be produced through circulating chemicals. That may be . . .

Dr. Barry Wilson, Chair

Can we insert circulatory and hematopoietic systems? Okay, why don't you just put in Circulatory. Let me ask something of the committee now because I, as a Californian, I can sense vibes. All right. Can we, it's now 20 after 4:00. Can we take 10 minutes for some of the folks in the audience who want things added, subtracted and things at this time? Have we got enough of a consensus amongst ourselves. Down, ladies. Wait a minute. Please, with the understanding now that we've had your input this morning and we put it in here. We may not take all suggestions. We didn't really take all of our suggestions. I don't want you to go away mad, but I think that it is important that I lay that ground rule down there. Okay? Because you can see just how hard we've tried. I haven't even heard the meeting today, trying to get this group forward. Are we

agreed that we'll take, say until 4:30 now, for a go around and then come back to ourselves and see, should we get an exchange going? Look now, no speeches. Just short stuff. You guys will all get there.

Audience Member

Since we're getting so specific, I just respectfully request that the vaccines have their own little number and put vaccine and adjuvant research instead of lumping together drugs and vaccines.

Dr. Barry Wilson, Chair

Are we agreed? [Agreement from the panel]. Now, you guys agree.

Dr. Peter Spencer

Do you want to make that language more specific and say investigational vaccines or just say vaccines in general?

Audience Member

I don't think so because squalene could have been in vaccines that were not investigational, like the flu vaccine and diphtheria and tetanus.

Dr. Peter Spencer

What are you concerned about with regard to squalene?

Dr. Claudia Miller

Induction of autoimmune disease.

Audience Member

Yes. That it produces the T-cell study responses and autoimmune disease.

Dr. Barry Wilson, Chair

For the future, let's set these down, I see a long list of people now. I am not going to go in with a laundry list tomorrow because I'll be taken out to the wash. So, the suggestion of the Colonel was we now make a list of the suggestions that each of you have and then we will go over them in our session again. Okay? I think maybe that is a better approach.

Dr. Beatrice Golomb

Animal Studies are on the list, and the problem that we have with existing animal studies is that we need to use higher doses in order to detect the more extreme outcome measures that we're required to use for animals since we can't ask them about symptoms. I respectfully suggest that we put some effort into detecting objective markers that correlate with disease such as those that some groups, like in Texas, are looking for. Because that will greatly facilitate our use of lower drug studies.

Dr. Barry Wilson, Chair

What would you want to call this? No speech. Just what would you like to call it?

Dr. Beatrice Golomb

Right. I would like to call it exploration for specific objective physiological and neuropsychological measures.

Dr. Barry Wilson, Chair

I thought that's what we had in our biomarkers.

Dr. Beatrice Golomb

I did not see it there.

Dr. Barry Wilson, Chair

It's there.

Dr. Beatrice Golomb

Where?

Dr. Barry Wilson, Chair

Never mind. I'm not going to argue with anybody if I can help it. Physiological markers, right?

Dr. Beatrice Golomb

Objective physiological neuro . . .

Dr. Barry Wilson, Chair

Well, if we're not doing objective ones, none of us should be up here. It's physiological markers.

Dr. James Romano
Deputy Commander
US Army Medical Research Institute
Institute of Chemical Defense
Aberdeen Proving Ground, Maryland

I support the research work, if only in a very indirect way, in areas of the possible role of chemical agent exposures as a causative factor in Gulf War illness. I've been torn by the problem of being open-minded and very inclusive, and I know that's the purpose of this meeting, and the fact that I do know that, in the end, there's only a finite number of dollars to support the research. I think this very prestigious panel perhaps needs to go one step beyond, if you can hammer out, perhaps in some break time, but I think you really need to, in order to best serve the veterans at this meeting, prioritize to your best estimates as to those areas that are most likely to yield benefits in research. I say this for a couple of reasons. One, many, if not most of those areas, are already covered in the broad portfolio, and so what we're saying here is we believe each of these needs to be made more adequate. But I think that none of you would imply that they are equally of importance, and that I think you should contribute a little bit more to this charge than simply this laundry list. Because I think at this point, the list may be counterproductive. It may be too big to be approached within the budget that's available. And I don't know what that budget is, by the way.

Dr. Barry Wilson, Chair

We don't want to know what the budget is, but thank you very much; and prioritize, I have tried to duck out of it. We have a final meeting tomorrow and this committee can each consider what we come out with today as we think about it tomorrow. Yes, sir.

Dr. Mamoru Shoji
Associate Professor of Medicine
Emory University School of Medicine
Atlanta, Georgia

I was in the treatment workgroup, not in here. I found this one thing missing on that list which is most important to me. In order to correlate illness and etiology, you need to determine what is the etiology that is a chemical. I would like to suggest to take, for example, veterans, just to take a biopsy of fat and extract the chemicals and try to measure the chemicals. What's in the chemicals. Because that is maybe different, but unless you determine what chemical veterans have

in the body, you cannot correlate any symptom or anything. Because all those are the result that the chemical exists.

Dr. Barry Wilson, Chair

Thank you, sir. Body burden and chemical analyses of vet biopsies.

Mr. Craig Stead

In the petroleum classification, I would suggest the examples would be solvents, fuels, Kuwaiti crude. And under the oil fires, the two major toxins I believe are soot and oil rain. And I would suggest those be added after oil fires in parentheses.

Carol Picou
Mission Project
Toccoa, Georgia

I'm a Persian Gulf veteran. I see one close to my heart, depleted uranium, because I know I was exposed to depleted uranium and I tested positive just from inhalation and ingestion of the particles. But, what I don't see up there is, under depleted uranium, you should test it for the chemical toxins of it and the radiation effects of it. Because, my bones and joints are deteriorating. My thyroid is deteriorating, and that's part of radiation contamination. I just came back from Iraq from the scientific symposium and they have a high rate of cancer and leukemia. Our own veterans are dying from cancer and leukemia, and our babies and the Iraqi babies are also dying from leukemia. The children that were exposed 7 years ago are now 12 years old and they're in the hospital dying from this leukemia and cancer. Our high concentration of leukemia and cancer in our veterans has increased in the United States also, there is a high concentration. So, depleted uranium should be studied for the effects of carcinogenic effects, the chemical exposure and radioactivity. I went back in 1997. I climbed on the same tanks I discovered during the war and they were still radioactive 7 years later.

Dr. Barry Wilson, Chair

Ma'am, we intended, when that was put in, we could write a whole sheet of only on DU, and we don't . . .

Ms. Carol Picou

I know. But, you still need to study, specify chemical and radiological.

Dr. Barry Wilson, Chair

You want us to specify more. Thank you. Okay. You want us to specify chemical and radiological consequences, effects.

Dr. John Ottenweller
Research Physiologist
Department of Veterans Affairs
VA Medical Center
East Orange, New Jersey

Peter didn't quite have my idea right, and it relates to the preamble, and that is 80 to 90 percent of your list could come out of the NIH talk that was in '93, the NAS Study, and all of the Gulf War meetings where they've asked us to do the same thing. I think you need to make a strong point that these priorities that you're trying to establish have been ignored. Because those were the same priorities they described 6 years ago and they haven't funded the work to get the answers related to those projects. Unless you start something up front with the preamble or some other way, then it's going to go into the same folder and be ignored in exactly the same way that the other recommendations have been.

Dr. Barry Wilson, Chair

There was an overhead that showed the existing grants that at least we had available to us here. One of the ways of prioritizing is to indicate which areas are supported. But you have to remember that one grant doth not a discovery make. So that, what Colonel Romano has laid on us, the task of prioritizing, becomes very difficult if the past priorities have been ignored, we invent the same wheel because it's not rolling anywhere.

Dr. Claudia Miller

I wonder if some people who are very familiar with all the past research can help us, by tomorrow, kind of weed through the areas that have had been heavily explored versus other areas.

Dr. Barry Wilson, Chair

We help ourselves here. We can do our job.

Dr. Claudia Miller

Yes, but there are some who are real knowledgeable.

Dr. Barry Wilson, Chair

It's 4:30 now. Can we hasten along? I have to keep you guys in line.

Dr. John Rossi

This is like real quick. As far as the Colonel's sand thing, I don't think you have that exactly the way you want it. Right now, it says fine sand or something. I really don't think people are really worried about silica effects, are they? What you really want to say is either dirty sand or you want to talk about things that are absorbed onto the sand and that are aerosolized into the point where they have become respirable.

Dr. Barry Wilson, Chair

Sand contaminants?

Dr. John Rossi

Yeah. I think you want to get across the fact that the contaminants, which are respirable because they're attached to the sand, is important – not the silica in itself.

Dr. Barry Wilson, Chair

Contaminated fine sand. Thank you.

Audience Member

Under other projects, recommending development of inexpensive tests for detecting sensitive sub-populations identified as part of the NIH's Human Genome Project. I'll give you a scientific paper, this was my proposal to NTP in 1993.

Dr. Barry Wilson, Chair

What do I do with that, now? Send it out for review again?

Audience Member

Put a line item and say liaison to the NTP program, we need these tests to identify sensitive sub-populations.

Dr. Barry Wilson, Chair

It's called a sandbag.

Dr. Ruth McGill

A couple of, several, three overall overview suggestions. First, I concur that we should separate our original contributions to new research planning from the on-going research that has been specified by other earlier meetings. This includes most of the bullets under exposure and under human. This will make it easier for our chairman to read to the room and more interesting for the room to hear.

Second, under human, similarly, we've got five bullets that refer to the physician's standard review of systems. The military and VA CCEP are also set up this way. I don't think we can get away with listing just five out of the total without offending somebody, unless we justify it with a heading, separate these five out, or the simplest thing would be to simply add another bullet that says other, other systems, other organs.

Third, in the preamble, I personally very much enjoyed hearing the panel concentrate on the mechanisms, and especially unifying mechanisms, cross-disciplinary mechanisms, and mechanisms that connect all of the difficult areas that we have listed – our seven areas. I'd like to have one sentence in the preamble that refers to this unifying mechanism. I'd also like one sentence to get the room, the entire convention, to sympathize with us for our extreme frustration. I think this has been a very difficult, confusing ordeal for all of us. And I think that the panel that we just heard, the methodologists also spoke to that, that this intrinsically is a very confusing, difficult, slippery disease that we've got here. We don't have a new disease. We have, probably, a new specialty. I'd like a brief reference in the preamble to our difficulty and our opportunity to expand and enlarge.

Dr. Barry Wilson, Chair

Thank you.

Dr. Leslie O. Simpson

Mr. Chairman, I thought that one of the purposes of the meeting was to help vets get an idea of what is the problem, what is their health status, what is causing their problem at this time. Now, what comes across is almost a wish list of the interests of the panel – maybe these are things we can get involved in investigation. There is no separation into etiology or pathogenesis. You seem to be providing a mechanism which says there are multiple etiologies, there are multiple pathogeneses, and there is no Gulf War syndrome. Now, the primary point that I would make is there is a list there which says hematopoietic studies. Now, I'm uncertain what this implies, but it certainly doesn't relate to the blood flow work that I have been doing with Gulf War vets.

Dr. Barry Wilson, Chair

Thank you, sir. We thought it did.

Dr. Shlomo Seidman
Hebrew University of Jerusalem
Department of Biological Chemistry
Jerusalem, Israel

One thing that for me is absent in the document which you have prepared, which may be self-evident, but I think might be worth speaking out, is a list of the objectives of the research that is being proposed. I think, I could suggest several objectives which I understand from the list. Maybe the panel could suggest other ones. They would be to identify precipitating events or agents leading to Gulf War syndrome; to identify mechanisms leading from the precipitating event to the onset of symptoms, to identify biochemical or physiological basis accounting for Gulf War syndrome, and to prepare the theoretical basis for the development of treatment strategies. I think if that would be specified at the beginning, it would provide an umbrella for all of the recommendations.

Dr. Barry Wilson, Chair

Thank you very much. One more.

Dr. Arnold Gorin
Director, National Referral Center for Gulf War Veterans
Department of Veterans Affairs
Baylor College of Medicine
Houston, Texas

I would request that 2(a), to the deployment cohorts, you perhaps add an 'other specially defined populations.' Examples would be the fact that in the National Health Survey of Gulf War veterans, Part III, there will be a population of 2,000 patients with nerve conduction velocity studies. It would be very interesting to look for Dr. Soreq's polymorphisms in those patients who have nerve conduction velocity abnormalities. Six hundred patients have been through the national referral centers in the VA and more if you consider the military's UCAP program. It would be interesting to look for polymorphisms in those who have elevated CBKs. And so, there are defined populations which should be studies besides the deployment cohorts.

Dr. Barry Wilson, Chair

Okay. Thank you. End of discussion for the moment. Quickly, because I think we need to get back. And then there'll be some more . . .

Dr. Robert Haines
President, Aurum Co.
Orange Park, Florida

Two suggestions. You might want to consider alphabetizing for the purpose of not showing any priority system for today. Tomorrow then, you can prioritize them. That may be helpful. And the other suggestion is, stick to either illness or syndrome, but don't intermix. In other words, we can call it Gulf War illness, if that's what it is, fine, or Gulf War syndrome. Just from a literary viewpoint.

Dr. Barry Wilson, Chair

Okay. Thank you. We now have a small watershed for us here. We could take a 5-minute break and stretch. I see people nodding, maybe. And then consider these suggestions and let it digest a bit, to incorporate or not, without ticking people off. We're going to do our best. But, something I want to leave us all thinking about is, we have skirted the issue of whether there is a single etiology or not. Believe me, this is a deliberate skirting because I think it is very controversial and I didn't know if we were prepared to launch ourselves out into that when we are recommending research, that may be a wine before its time. So, with this, let's take a 5-minute break. Thank you.

[*After the Break]*

Dr. Barry Wilson, Chair

Okay. We're convening here again for a short time, I hope. A few suggestions I picked up for the record that are very good. One way to consider priorities is for interdisciplinary research. The audience and the panel must all be aware that we know we have reinvented the wheel. Why we've done that is we do not have in our hands the lists of all the research that has been done. I propose that tomorrow, I report that what we're interested in is in prioritizing research that will shed new light on the objectives that we will have, and on interdisciplinary research, and that we recommend that these research suggestions that we make be filtered through the existing programs and support, because this information was not available to us at this time. That's why it looks like a longer list than it would end up to be.

But, that has to be very carefully considered when you go over and look at the research projects because the titles do not always say what they are, and doesn't always say what the accomplishments are. Sometimes it's very important to do some things over and over again. So I'm putting that part of this on the table as we get toward this. We have another meeting tomorrow before it's finalized. So, we have time to think of short- and long-term research items here, think about condensing some of the list, and now about some of the suggestions that were

made where we took them down as a list here, and now see whether we will incorporate them or not. If not, remember that we disagree but do not want to be disagreeable.

I tried to jot some of these down. The first one I have here was to get in that we are interested in physiological markers, that somehow we're dealing with the human body and its function. Does the committee agree that that kind of phrasing is important to emphasize and get in there?

Dr. Peter Spencer

I would just call it biomarkers of susceptibility, exposure and effect. At the present time, you have biomarkers of exposure and effect.

Dr. Barry Wilson, Chair

Biomarkers of susceptibility, exposure and effect.

Audience Member

Doesn't that mean illness?

Dr. Barry Wilson, Chair

Yes. Okay. Second was for us to prioritize, and somebody asked, though, that specifically we do biopsies of veterans and do chemical analyses of those biopsies. That's a very complicated situation and that is, may or may not be likely to say something, and I would, my feeling is I would punt that one.

Dr. Claudia Miller

Since we're an etiology workshop or workgroup, it seems we need to consider now some hypothesis driven kinds of etiologies, and to talk about biomarkers generically is fine and certainly important. At the same time, I think we're in a place where we should talk about what potential etiologies could or need to be explored further. We know some have been explored quite a but. But, to prioritize potential etiologies that could be explored in great depth, and whether we're going to pick a handful or whatever, but things that, I think Dr. McGill pointed out, potentially offer a way of unifying the diverse symptomatology and health problems the veterans are reporting. It doesn't mean you have to do that, but if we could think of some that would do that that haven't been explored already, those would seem to be important.

Dr. Barry Wilson, Chair

Okay. You caught the ball when I punted. To do just a chemical analysis, s shotgun of residues, can we deal with what this issue is? Does anybody have any suggestions?

Dr. Peter Spencer

Well, conventional wisdom would be that you would only find organochlorine and other lipid soluble materials in fat biopsies. The only organochlorine to my knowledge that was used in the Gulf was Lindane, and that was used only in a relatively small number of . . .

Dr. Barry Wilson, Chair

Is there a way that we can include in here the ability, in other words, I'm trying to get it under the umbrella somehow, because certainly one of the biomarkers is to do biopsies.

Dr. Peter Spencer

Well, it's a biomarker of exposure if you want to look at it from that point of view.

Dr. Barry Wilson, Chair

A quick suggestion, not a lot, please. I know you had made the suggestion. Wait a minute, the guy in the back first and then . . , I am falling into this trap again of arguing with you guys.

Audience Member

We need some consideration of the concept of dose as opposed to exposure.

Dr. Barry Wilson, Chair

Some of us that do biopsies in chemical residues get very bothered about promising things we can't deliver. So, what kind of suggestion have you got?

Audience Member

I think the concept of differential susceptibility is probably important. I think it kind of subsumes all the different etiologies, because I'm starting to believe that there are definitely, at least in my mind, now more than one. And I think, obviously, since not all people were affected and people were differentially affected, there has to be something to that. So, I think just the concept of differential susceptibility.

Dr. Barry Wilson, Chair

Let me do something right now. We will come back to you, sir. I want to table this one to go down, let's do the easy ones, then come back, as a group, okay? Next one down. The next one was to say solvents, fuels, and Kuwaiti crude oil, soot and oil rain. That's incorporated already. That's done. Okay. Been there, done that.

Dr. Peter Spencer

There's a lot of redundancy there, frankly.

Dr. Barry Wilson, Chair

Well, let's let it go right now and move on for the sake of this. The depleted uranium – wanted it to be more specific, talking about the effects, the toxic effects and radiological. Yeah, toxic and radioactive effects. Do we wish to add that? [Many endorsements from the panel]. Okay, we're agreed. So, that gets added - toxic and radioactive effects, depleted uranium (toxic and radioactive effects). Done. Now, the next one I can't read. Something was ignored. What was ignored? Nobody can read my writing. I should have been a real doctor, I could do prescriptions. I'll junk that one and go on to the contaminated sand. We still haven't phrased the sand right because we were trying to get it short and sweet.

COL Andras Korenyi-Both

CW agent saturated, contaminated fine sand.

Dr. Claudia Miller

Some people are thinking of other things like animal droppings. Bird droppings and stuff.

Dr. Peter Spencer

How about pesticides and insecticides?

Dr. Claudia Miller

Just say, Contaminated. We don't know what was in it.

Dr. Barry Wilson, Chair

What transpired here is I . . .

COL Andras Korenyi-Both

Excuse me. Contaminated and saturated are two different entities. So, in case if we are not using contamination, but we use saturation, then we can put CW agents saturated.

Dr. Barry Wilson, Chair

Okay. Well, I would agree that it could be more than these CW agents that we worry about if there's some really bad stuff in that sand. I would favor leaving it just contaminated for now, it's inclusive. I'm going for an umbrella to keep off the rain. Next, again to separate out the new things, and that's, we will try our best but we don't always get there. The other is the other organs. In trying to provide a breakdown from molecule up to the environment, we got trapped in an organ system listing because those are the major ones and somebody said, "Well just put in other organs." Have an E, none of the above, and Dr. Soreq is nodding. So long as we have too much already, one more won't hurt. Okay, other organs. If somebody discovers another organ, we'll be right there. The preamble, we are working on. The idea that we really represent a new specialty is really, as I said earlier, if we say we're putting priority on interdisciplinary research, and it really gets done, we will have invented a new specialty.

COL Andras Korenyi-Both

Can we go back to the other organs, and for example put in the reticuloendothelial system.

Dr. Iris Bell

I hate to do this, but we have lost the concept of systemic effects like fatigue, and that certainly is a leading symptom. So, we have to find a way to make sure that's expressed.

Dr. Barry Wilson, Chair

Yes. Please think about that while I go through these because, certainly, the whole idea of behavior is important. Somebody said we needed to separate etiology and pathogenesis. That brings us to whether we want to say there is more than one etiology. And I do suggest we punt, because we'll have to, by tomorrow, have this narrowed down even more than we have now. Dr. Soreq.

Dr. Hermonia Soreq

I like your idea about interdisciplinary. Why don't we add that to the objectives?

Dr. Barry Wilson, Chair

Yes, or up in the objectives, too. Do it both places - prioritizing interdisciplinary research. Okay.

Now in 2(a) somebody wants to put in other specially defined populations. It sounded like a winner. In number 2(a), it says analysis of deployment and other defined cohorts. Okay. Blood effects mentioned by Dr. Simpson. He came all the way from New Zealand and he's got something important to say. Okay, now let's see. What was the one we punted that we were going to come back to? [Comment inaudible] Yeah, I thought that was under genetic screening.

Dr. Peter Spencer

Except there are other sensitivities, including aging and nutritional factors, which can dramatically impact susceptibility. So, gender, we have gender in there, we have genetic in there. We don't have age and we don't have nutrition.

Dr. Barry Wilson, Chair

Okay, let's hold up for a minute because I've gotta be honest here. I had on the biopsies and chemical residues, a proposal of the gentleman from the treatment workgroup. Now, how do we wish to phrase that so it does not put us into discovering chlorinated hydrocarbons?

Dr. Mohamad Abou-Donia

What about morphological studies?

Dr. Barry Wilson, Chair

Pathochemical morphological studies?

Dr. Peter Spencer

Mr. Chair, why have we gone from susceptibilities to talk about fat biopsies?

Dr. Barry Wilson, Chair

Oh, because that had not, oh I see, you mean we hadn't finished the other. I'm showing some stress.

Dr. Mohamed Abou-Donia

Barry, I don't think it will, 8 years after exposure, find any organic chemical in the body, not in the fat, not in the tissue. The only thing that you might find actually, might be depleted uranium in the bones. But I don't think we'll find it in the soft tissues. There is nothing that would stay there more than a few months.

Dr. Barry Wilson, Chair

The biopsies should and can be taken in those human subjects where we proposed it. But, sir, yes, speak, speak quickly and briefly to it.

Audience Member

This is, yes, we are not talking about classing, or conventional wisdom, or anything. We are talking about the science. Science is you got determinant. You've got to measure the determinant. You are saying a hypothesis, maybe not there, but the treatment group, we have a, you know, that Sacramento, California a big clinic treating the detoxification program. And that suggests that they are detoxifying something in their clinic. And, therefore, it is suggestive that some toxin is still there in the body. And, therefore, we should determine what's in there and learn about it. Let's look at number 1, environmental things. If you have a given patient to look at, that is our statistics. You are talking about environmental exposure history, but you may or may not have a relevancy to that patient. So, it really can't help that information to what's going on in the patient.

Dr. Barry Wilson, Chair

Sir, now that I know what you are saying. I would suggest that the treatment group do this to validate a treatment that is being proposed and is being raved about. That, we're not driven by any physiological hypothesis here about that treatment group at the moment. I know I'll catch a lot of flack.

Audience Member

No, no, no. I'm sorry, I came to this group because you are looking at the etiology or pathophysiology of illness. In order to really correlate symptoms to pathophysiology, you need to have demonstration of an etiological agent. That's what I'm getting at.

Dr. Barry Wilson, Chair

We have not excluded that that be done here. But neither have we said that every Gulf War veteran has to have biopsies, and a major work-up. Do you want us to look at dioxin? It's $1,000 minimum – one sample.

Dr. Peter Spencer

Barry, the gentleman is not asking that I don't think. I think it's a reasonable suggestion. If I could just speak in support of it for a moment. The whole issue of detoxifying in the clinical

setting is highly controversial. The majority of the clinical community doesn't give it the time of day. If the veterans believe that something is being removed from the body as a result of this process, it will be a simple matter to demonstrate whether that is true or false. And to the extent that it would move us on in our research agenda, I think it's a reasonable suggestion for that very narrowly defined population.

Dr. Barry Wilson, Chair

So how do we phrase it? Would it be phrased as chemical analyses of detoxification programs or something?

Dr. Peter Spencer

No, just clinical verification of detoxification, perhaps.

Audience Member

I would like to phrase it just chemical analysis of a fat pad of Gulf syndrome veterans.

Dr. Barry Wilson, Chair

Yes, I know that's the way you'd like to phrase it, sir. But, we are still discussing.

Dr. Deborah Norris

And I thank this gentleman for bringing it up, Mr. Chair, because during our 5-minute break I went down to the treatment group and I keep learning things at this meeting. They're addressing what treatments work, what treatments should be used. They're not addressing why treatments work. My background is in pharmacology and psychology, and I've seen a lot of instances where, looking at why treatments work explains the etiology. Depression - we use many antidepressants, we have in the past. We had no idea why they were working, and when we looked at why they were working, when we found the tools to understand why they were working, we started to understand the etiology and the mechanism of the disease.

Now, what I'm not providing right now is exactly where you want to fit that in. If you want to put that in humans, if you want to put that in the preamble, if you want to use that as something cohesive to tie all of our work together. But, I know that Congressman Sanders emphasized, and I hear these veterans out there. They're not in here, well there's a few here, but there's a lot of them down there in the treatment group. What they want is treatment. And, if we can provide information on why those treatments are working, then . . .

Dr. Barry Wilson, Chair

And I have a phrase - it's analytical verification of detoxification.

Dr. Peter Spencer

As an example of a cross-disciplinary activity.

Dr. Barry Wilson, Chair

And that includes fat pads, but need not be only fat pads. There's a lot of other parts of the body to look at. Is this getting close - analytical verification of detoxification processes? Or what? Because we're dealing with processes, not somebody who set up a clinic.

Dr. Deborah Norris

You're presuming we know the treatments that worked. I am referring to any treatments that work.

Dr. Barry Wilson, Chair

Well, so am I. I'm just saying they have a detoxification . . .

Dr. Peter Spencer

We can model this in animals as well.

Dr. Claudia Miller

Well, it might be mycoplasma being treated with doxycycline, too, I mean, you know, and you could try to test and verify whether or not you see changes before and after treatment. If you're trying to get into that, and it has value like you're saying, like yes or no.

Dr. Barry Wilson, Chair

What we're asking for is analytical chemistry to be brought to bear on these, and let's see, a quick one, because we've almost got this one hammered out.

Audience Member

I think it goes a little beyond analytical chemistry, though. I think, basically, what you're talking

about is research strategies which are driven by successful treatments, you know, in general.

Dr. Claudia Miller

Treatment driven research instead of exposure treatment.

Dr. Barry Wilson, Chair

Now that's an open-ended one. In other words, the other way around, which is fine by us. Usually, you cure some before you know how it works. We'll take any door if it's open.

Dr. Claudia Miller

And it happens all the time.

Audience Member

What about analytical procedures to determine exposures? Because the question he was talking about was chemical residues in the body. If you have oil in your lungs, it should be in granulomas and paraffinomas, under biopsy this can be extracted, and you can actually. I have been told, fingerprint it to Kuwait crude. I would take that would a big grain of salt, because as you have said, you can promise a lot of things and deliver very few.

Dr. Barry Wilson, Chair

Let's reform. We don't have, under our exposures there, P should be that we should support improvement of analytical methodologies for exposures, better analytical chemistry for all of these things that we want, so how do we put that in? It could come under P, on the top one, because it's not only the human we're talking about. Or it could come all the way down at the bottom where we talking about some special needs, and we're now asking to get some special chemistry.

Dr. David Ashley

Are we talking about biomarkers of exposure there?

Dr. Peter Spencer

Exactly.

Dr. Barry Wilson, Chair

I don't know. We might also be talking about detection of things out in the environment, too. You see, I'm trying to enlarge it. Where do you want to put it? I think we're agreed we want chemical analyses when they need to be there. I didn't get down properly what was said about research strategies to accompany . . .

Audience Member

Driven by successful treatments.

Dr. Barry Wilson, Chair

She's got it - research strategies driven by successful treatments. Okay. And now, we want analytical studies, no, well, I guess that covers the detoxification program. But, now we want somewhere to improve the analytical chemistry. Of what? Biomarkers? Environmental contaminants? That's under methodology.

Dr. Peter Spencer

Why do we want this, Barry? I mean, analytical procedures are far in advance of our ability to know what they mean. We can detect down to parts per trillion . . .

Dr. Barry Wilson, Chair

Okay, so we've come full circle, and the analytical chemist got in through the fat pad, but they didn't get the whole show. Now, that takes care of that list. It is just about 5:30. My suggestion is to have this printed out and you guys, don't go away until it is printed, and each of us take a copy. Be ready tomorrow, where we tie up the preamble, think about short- and long-term. The preamble has in it now the disclaimer that this list has to be filtered against existing against existing programs and sorting out priority for new and interdisciplinary research. Claudia.

Dr. Claudia Miller

I know what I'm going to say is not going to be very popular with you, but we are an etiology workgroup, and I think this question of whether there are unifying mechanisms here that would go toward explaining this that we should be looking at that we haven't examined before, is a critical issue.

Dr. Barry Wilson, Chair

So, you want us to also say we will support science driven proposals to establish unifying mechanisms for Gulf War problems.

Dr. Claudia Miller

Particularly if they explain the delayed effects and unexplained illnesses of Gulf War veterans.

Dr. Barry Wilson, Chair

I'm trying not to say Gulf War syndromes - illnesses. Do you have that Sheila? Where does it go? I just forgot it. Unifying, say it for me Claudia.

Dr. Claudia Miller

Unifying mechanisms that would explain the multi-system and delayed systems . . .

Dr. Barry Wilson, Chair

No, no. That's not what I mean by unifying.

Dr. Claudia Miller

That's what I mean by unifying. What do you mean by unifying?

Dr. Barry Wilson, Chair

Well, we want to support research, science driven research on unifying mechanisms to understand the Gulf War illnesses. It can go right under special needs or anywhere, we'll fit it in. That's the preamble, because it's a priority we're giving. We're giving priorities to research on unifying mechanisms. [Simultaneous discussion]. We have enough now so that the committee will be able to come back tomorrow, tie this up, think of short- and long-term work, and unless Dr. Spencer's finger comes down . . . I was moving for the exit.

Dr. Peter Spencer

With regard to previous research recommendations, an observation has been made by a member of the audience, and sort of built upon by myself, that the first research recommendations relating to Gulf War unexplained illness was made by a group of civilians who was assembled at the NIH in1994. Thereafter, the research recommendations were taken under the umbrella of inter-agency federal Group, the Research Working Group, which I believe has a membership from the DoD, the VA, the EPA, and the NIH. Is it time to reconstitute a civilian sector advisory group? This is what we are. Is there any merit to considering some longevity to repeated civilian sector recommendations?

Dr. Barry Wilson, Chair

Now, this would be in the preamble, the recommendation that we're suggesting there be civilian . . .

Dr. Peter Spencer

To parallel the federal Research Working Group, there might be a civilian scientific group.

Dr. Barry Wilson, Chair

Some people are saying "absolutely" here. Could you phrase that tomorrow?

COL Andras Korenyi-Both

I would put it to the veterans.

Dr. Iris Bell

NGO is the term - non-government organization.

Dr. Barry Wilson, Chair

Peter is charged with that for tomorrow.

Dr. Claudia Miller

When you deal with superfund sites, they constitute groups of people who have expertise, scientists and community people. So, I think that same format here, having some meaningful representation from the veterans' input, however that would work, and some expertise from outside of VA, DoD, etc. would be very good. I like that.

Dr. Barry Wilson, Chair

They're supposed to by law. But, if we want, we could reiterate that we want to see, the horrid word is "stakeholders," of the Gulf War that will be a part of these considerations, too. Sir, okay, one statement and then we're going to close.

Audience Member

Where you put, I think about treatment driven research strategies, nobody's going to think about

to measure chemical levels from a fat pad. I think that's . . .

Dr. Barry Wilson, Chair

Sir, thank you very much. We are, the committee does not seem to be dealing only with fat pads. I'm sorry. It didn't sell that strongly.

Audience Member

But, could you put in chemical analysis, what chemicals are in the veterans. You need to determine the causative agent.

Dr. Barry Wilson, Chair

Let us think about this for tomorrow, okay? I want to thank you all. First of all, you guys have stuck here and stuck it out, and the committee has. We may have too long a list. But we have a list. We have tomorrow morning. Dr. Spencer's going to give us one hell of a preamble. Sheila Newton and Dr. Abou-Donia have done a lot of work to get us to this point, and I suggest that we thank them. I want to thank all of you as we adjourn until our morning meeting tomorrow. Our last meeting together.

The session was adjourned.

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Day 3 – Tuesday, March 2, 1999

COL Andras Korenyi-Both

Mr. Chairman, before we start with the business, I have a motion for recommendation. I would like to recognize you as our chairman for your outstanding work, how you were trying to ride on a tiger, which is very hard to do. Sir, we very much appreciate your efforts.

Dr. Barry Wilson, Chair

Thank you all very much. My one advice is when you get to ride a tiger, make sure you know which direction you are sitting on. We come to the conclusion of our endeavors. I'm afraid it's actually the end of the beginning, not quite even the beginning of the end, because what you've learned to see here is multi-disciplinary research and our struggles as disciplinary scientists to pull it together. A few more days, and we might have been able to meld this, so you couldn't tell a psychologist from the cell and molecular biologist. That unification is yet to come. The audience has immensely helped us. At the same time, it's made our job so much more difficult. We could have given you the research to do in one hour here, and you wouldn't have liked it, but we would have been out the door. This way, we've had to learn. I've learned much more than the rest of you, these last few days, and I'm not finished yet, but I want to thank you all for your patience and for your good humor with us.

Our agenda is to look over what we've done. It was pointed out that in the document that all of us got, and I'm going to pass this around, there's something that sets the tone, and you can see that we were getting to this. Then there's a preamble that has been prepared mostly by Peter Spencer, but with input from Dr. Soreq and myself and I will read that, because this is what will go forward. Let me read this and this is part of our charge.

A central question to be addressed by Workgroup 1 is what are the most plausible etiological hypotheses concerning diagnosed diseases, unexplained multiple symptom illnesses noted among Gulf War veterans? Associated questions include are on-going research projects addressing the most plausible of these hypotheses. If not, which additional plausible hypotheses should be addressed? Are there research methods or approaches that need to be developed or that are available and are not being used?

The Gulf War experience has created intense interest in the health effects of particular chemical agents such as depleted uranium, organophosphate chemical warfare nerve agents, carbamate prophylactic agents against organophosphate nerve agents, vaccines and organophosphate pesticides. This interest leads to additional questions within the focus of Workgroup 1.

We have really tried to address as much of that as we could in this short time, I think. I know I feel if asked, and believe me, I have been, in the hall, but we've pulled together the best job that you're going to see right now, because this is only an hour, and then we go on. It's show time. The preamble, which is now for the committee to consider, okay? You guys don't have to agree with it, but, it's a synthesis of agreements we had yesterday that are not those of the specific pieces of research. The general agreements, particularly one part, you'll see here.

The framework for a national agenda of research on illness of Gulf War Veterans was originally developed in 1994, by non-governmental medical scientists in an NIH consensus conference. In subsequent years, additional recommendations were made by various non-governmental committees, notably, the Presidential Advisory Committee and the Institute of Medicine. These inputs have been used by the federal interagency Research Working Group on Gulf War illness to develop and implement a national research agenda. The present research recommendations are built on this foundation, however, they arise primarily from the combined input of veterans and non-governmental medical scientists.

The recommendations are intended to provide an additional source of considered judgement on an appropriate research agenda that responds to current and future health needs of U.S. Gulf War veterans. It is recognized that there is overlap between the present research recommendations and those noted by previous groups. Moreover, a significant portfolio of research is already underway, and the fruits of this investment are only now beginning to appear. Some earlier research recommendations have not always been followed. The present list of recommendations is the best current estimate of areas that merit research investment, whether ongoing or yet to commence. It will be necessary to compare this list with previous recommendations and ongoing research to determine areas that are newly identified. Prioritization of research among existing and newly identified areas, must take into account the limitations of available funding and the pressing need to obtain scientifically sound answers to address the health needs of veterans at the earliest possible time.

An overarching theme that arises from these recommendations is the synergy and the benefits that result from interactive research among medical and basic research scientists and veterans. To maximize the chances for success, it is imperative that scientists listen to the experiences of the veterans and attend to their needs. It is also of critical importance that veterans encourage and support research directions reached by this consensus. It's a two way street, guys. The research agenda, whenever possible, should be interdisciplinary, for the combined activity of the basic and clinical scientist is required to move from the bedside to the bench and from the bench to the bedside. Research should be focused on unifying mechanisms that explain etiology, pathogenesis and treatment of unexplained illness.

To ensure an enhanced continuation of the present cooperation between health professionals and veterans, it is recommended that a non-government national Committee be established to advise

on the selection and implementation of these research recommendations. This is not intended to replace the government interagency Research Working Group, rather to provide a mechanism by which the interests of Gulf War veterans can be heard on a continuing basis by a non-governmental group.

A possible venue for this committee is the National Research Council, a non-governmental body with a reputation for independence, with joint participation among the National Academy of Sciences, the Board of Toxicology and Environmental Health Hazards, the Institute of Medicine, including the Medical Follow-up Agency, and representatives of Gulf War veterans' organizations.

The United States took the lead in activating research on Gulf War veterans' illnesses and was later joined by other countries within the coalition that fought Iraq. Early opportunities for international collaboration were missed. There is little information on country-specific prevalence of unexplained illness among veterans and why some coalition partners were spared. Little or no research has been undertaken among the communities directly impacted by the Gulf War conflict and no international public health research has been carried out in Iraq. For a clear picture of the relationship between the adverse health effects of environmental exposures in the theater of war, it is imperative that every conceivable opportunity is taken to collect and synthesize relevant exposure and health information from other nations, including both allied countries and Iraq. Because veterans of all communities participating in the Gulf War sustained exposures of concern, there is no scientific basis for exclusion of one party from study. The medical doors of Iraq now appear to be open to international medical scientists committed to finding answers to common health problems. Credible evidence of a rare disorder occurring in high incidence among Iraqi veterans, could greatly impact understanding of a comparable illness among veterans of coalition forces.

The research recommendations include a mixture of short-term goals of immediate relevance to understanding and treating Gulf War unexplained illnesses and longer-term goals that will build the foundation to prevent and understand environmental disorders in future generations. The immediate needs are important and pressing, but the value of investing a portion of available research dollars in new methodologies cannot be over emphasized. Chemical and biological weapons have emerged from anecdotes in the history of human warfare to pressing current environmental hazards in both civilian and military sectors. Research on their mechanisms of action and the short and long-term adverse health of low-level and sub-lethal exposures have been recently recognized as national priorities.

I ask the committee now to consider what a small group of us have written. There are areas in here that stretch us out. This committee has not been just jokes. This is serious business we are upon. I do declare the war is over, and now we need to worry about the health.

COL Andras L. Korenyi-Both

Sir, I would recommend that we change the language in one line. In the line where, if I correctly recall, you express why certain members of the coalition forces were spared.

Dr. Barry Wilson, Chair

No, we didn't say why. We just mentioned that this occurred.

COL Andras L. Korenyi-Both

I would change the language that certain members of the coalition forces did not report.

Dr. Barry Wilson, Chair

Ok, I will read the sentence - There is little information on country-specific prevalence of unexplained illness among veterans and why some coalition partners were spared. The easiest way to do that is put in 'seem to have been spared.'

COL Andras Korenyi-Both

So, I would change it, instead of spared, why they did not report.

Dr. Barry Wilson, Chair

Either that, or, seem to have been spared, is the alternative I'm offering. There are two on the table, which one do you like? Both of them cop us out.

Deborah Norris, PhD

I kind of like what the Colonel said.

Dr. Barry Wilson, Chair

Were not reported?

Dr. Deborah Norris

Yes.

Dr. Barry Wilson, Chair

Now I go for consensus in the old fashioned way. (Asks the group to vote. They reach consensus on: *Why such illness was not reported by some coalition partners*). Okay, that's a change. Any other comments about the document?

Dr. Claudia Miller

While we are on this screen, I'd prefer not to specify the makeup or even recommend a potential makeup for a group. With Superfund agencies, people have constituted equal…balanced, selected people from the community and people who were chosen as experts, and I think you may want to be a little vague on this. I think there may be some very good ways to constitute it and I don't know that we would want to recommend, particularly the Institute of Medicine, which is already even involved in recommendations on research. I think that may not be viewed very well. The National Academy of Sciences may be alright, but I think I'd leave that out. Just talk about having some balanced representation.

Dr. Peter Spencer

If I could just respond to that? The National Research Council is an independent body which consists of the Institute of Medicine and the National Academy of Sciences and the committees associated therewith. I think we all feel very strongly that one needs fundamental basic science as well as medical science as well as physician input into addressing these problems. Because of the solid history the National Research Council, both arms thereof, and the respect with which they're held, I cannot think of another body in the United States which would possibly carry the weight which the National Research Council would carry in moving this forward. If the National Research Council were able to take this on and funding was obtained to support it, it would have instant credibility among scientists, and one would hope, among the public, and any reports that it would produce would certainly have clout.

Perhaps more importantly, federal agencies would listen. Federal agencies, including DoD, regularly have their research reviewed by the National Research Council and listen carefully to the deliberations, thereof. I would strongly recommend that we consider specifying where we think this should go.

Dr. Barry Wilson, Chair

May I speak to what Dr. Spencer has said and to point out, that the sentence starts out with a possible venue. It's an example; it's an example that I happen to agree with because I think the NRC is our best way, and why I'd like this to remain in, is that we have come a step up from what we we've doing. We're now dealing with real politics, we're making recommendations to help this whole business, and I don't want to stand up there and give people a problem, and not point

out a solution. You've got to have an example of where you can go. They may choose not to go that way, but at least we will have suggested, here's your problem, there's a solution. Each of us are disciplinary scientists, we've got to find a way we deal with the multi-disciplinary and multi-political problem. I've worked with the NRC too, and flawed or not, they're the best show in town.

Dr. Claudia Miller

I understand. I'm saying there may be other models than choosing something that's pre-constituted, and one could take veterans…the concern I have is that, in the past, when we've taken independent groups, like IOM, the people on those committees have had very little contact or experience with the Gulf War veterans' illnesses, and until you have scientists who have immersed themselves in this, and there are enough now with all of the different research and things that are going on around the country. If you take someone who's distant from the situation, hoping to get independence, you're also getting people who are not familiar with what's been done, what needs to be done, and you end up with something that is not very meaningful.

Dr. Barry Wilson, Chair

This is usually not the way the NRC functions. You are right, I agree with you fully, but the way the NRC does this, is they appoint a committee that's pulled in. They're just a kind of a body that pulls in these subcommittees, and the subcommittees are brought together and they are the experts of that area. That's why I have confidence that they would do it. They don't have a board of themselves that would do the job.

Dr. Peter Spencer

And they're people like you and I. We all serve voluntarily on those committees.

Dr. Barry Wilson, Chair

Several here have just spent some harrowing days on a risk assessment for low level chemical warfare. I'm not with the National Academy and at the rate I'm going, putting my foot in other people's mouths, I never will be, but I serve on the NRC.

Dr. Claudia Miller

Is there a model for having balanced representation of veterans, or their representatives on such a committee?

Dr. Barry Wilson, Chair

Why don't we say "a possible venue for this committee is through the National Research Council" instead of making it sound like they're the body?

Dr. Sheila Newton

I just want to point out, the NRC is not in the habit of taking on long-term standing investigations. They do short-term things, anywhere from six months to two years, and this, I think, will require something along the lines of a chartered federal advisory committee, and I'm not suggesting that. I'm just saying that it has to be something that would have a longer term than what the NRC is currently engaged in.

Dr. Claudia Miller

The VA, the advisory committee, the idea of having a long-term, ongoing committee for years, I think, is a very good idea, but the problem with a VA advisory committee, on which I have sat, is that we have very little input directly from Gulf veterans and very little testimony from them. And of course, these are people chosen by the VA, and I think there's a natural concern that veterans may have about that, at this point. So, I'm thinking like you are; why can't we have something long-term, and not, to me, the Superfund analogy is much closer. The stakeholders are people who need to have a balanced representation. We wouldn't be here at this meeting today if it weren't for concerns arising out of lack of adequate representation for the veterans. So, I think there's another model here, and the model I see, again, is what's used in communities with toxic waste dump sites where you have much more community involvement with education processes and everything else, and then, there's more acceptance of what comes out of that process.

Dr. William Suk
Director, Office of Program Development
National Institute of Environmental. Health Sciences
National Institutes of Health
Durham, North Carolina

Sheila's right. There are ways of establishing a mandated, sanctioned, if you will, committee together, by Congress and various offices of the federal government, HHS level, VA level or whatever, and the point is, I think you're analogy is well taken. When we established our Superfund basic research program and our worker training program, it was an advisory committee that was put into place with mandatory representation by local organizations, individuals, concerned citizens, government officials from various agencies, as well as academia and industry. So, there is a way of doing it through a sanctioned committee.

Dr. Barry Wilson, Chair

Okay, now apparently, we're all agreed that we want something like this. Are the drafters prepared to accept the suggestion for a mandated, if not Congressionally-mandated, committee and phrase it the way Bill was?

Dr. Peter Spencer

Can I just respond to the issue of longevity of these committees? The National Academy of Sciences regularly address the issue of pollutants in drinking water and has done over a number of many, many years with repeated publication of documents in this area. So, they do take on projects which have long-term importance and regularly turn over their committees to address this on a continuing basis, which is very healthy. I would suggest, as a compromise, that we offer the Superfund model as another possibility.

Dr. Barry Wilson, Chair

At this point in time, you will find, Peter did this very well, because he got there one sentence before I did, the way, when you reach a disagreement like this, you run off in both directions, because these provide models. We may not be able to be so sure of what it is at this point, but we know what we want, it looks like, and these solutions can be taken either way. Can you draft a statement quickly about this part and then we'll insert it?

Dr. Claudia Miller

Can we conceptually agree, whichever venue this comes under, that there needs to be a balanced representation between independent scientific experts and stakeholders, Gulf veterans? What I'm saying is, this is what we want, and here's some ways it might be achieved.

Dr. Barry Wilson, Chair

Okay. Bill, do you want to draft that while we're sitting here? Okay, any other, there is one other point here, Dr. Soreq's on now for some changes. She pointed out, when I read page 32, there was something to be addressed.

Dr. Hermona Soreq

We're embarrassed to find that we need to address the questions that were put forth by the CDC before this meeting was organized. So, the suggestion is to add a sentence - "To find out the most plausible etiological hypotheses concerning diagnosed diseases and unexplained multiple symptom illnesses noted among Gulf War veterans, the committee calls for the commencing of

multi-disciplinary research efforts." I mean, we all assume this is what we want to do, but actually, we've never written it anywhere.

Dr. Barry Wilson, Chair

Agreed.

Dr. Claudia Miller

Can you repeat the language that you would . . .

Dr. Hermona Soreq

I think it was probably the accent, and I can't improve on that.

Dr. Barry Wilson, Chair

Let's se if I can read it - "To find out the most plausible etiological hypotheses concerning diagnosed diseases and unexplained multiple symptom illnesses noted among Gulf War veterans, the committee calls for commencing" - I should say just - , "calls for multi-disciplinary research efforts."

Dr. Claudia Miller

I thought I saw 'multi-disciplinary research efforts' in there before. There is a little difference here though, we are calling for it, is that the emphasis? OK.

Dr. Barry Wilson, Chair

We're standing forth. It is a sort of motherhood statement but it's okay. We're standing forthrightly on this.

COL Andras Korenyi-Both

So, if I may project, this is a carbon copy of that area. I just broke it down line by line. I believe your recommendation is well taken.

Dr. Barry Wilson, Chair

Yes, but it doesn't hurt to be redundant on this point. Some of our friends will read every other line.

COL Andras Korenyi-Both

Should additional research resources be applied to support multi-disciplinary research?

Dr. Barry Wilson, Chair

You need the word in there, multi-disciplinary, because many people think multi-disciplinary research means to get four experts in four areas and put them in a room. Just like we've done here.

I must point out that, this is why I wish we had an extra day. Our time is running down, but I think it's okay if we repeat things. We haven't violated our charge, and we are trying to show people that we have dealt with it. Do we agree with Dr. Soreq's changes? Do we agree in principle with what Dr. Soreq said? It's going to be difficult not to, because it's in our charge. [Group comes to consensus]. Okay, then the way it is phrased now. Okay, there are still a few other changes to that, that I suggested to clarify by Dr. Spencer. In the part where we say that "it's imperative that every conceivable opportunity is taken to collect and synthesize relevant exposure and health information from other nations, including both allied countries and Iraq," there is a typo in there. And a sentence down the line, "the medical doors of Iraq," should say, "the medical doors of regional allies and of Iraq now appear to be open."

Dr. Claudia Miller

What evidence do we have for that, by the way?

Dr. Peter Spencer

One of the last speakers from the audience, I don't know her name, but a veteran who served as a nurse in the war told us of the story of how she attended a 1998 conference on medical issues in Iraq as I believe the only American participant among a group of international participants, which included Germans and people of other nations. Perhaps if she's in the audience, we could . . .

Dr. Claudia Miller

Carol Picou is who you're talking about, but I don't know of any official opening. I think she may have gotten through by using some very special means. Do you know?

Audience Member

She had to violate existing state regulations on passports in order to get into that conference.

Dr. Barry Wilson, Chair

Well that doesn't mean the door to that conference was not open, it means we need to recognize this. That's why we have the word "appear" in there.

Audience Member

We might have to encourage the government to help us.

Dr. Claudia Miller

I think so. It is hard to imagine the door is open with all the baring of aid. I think that would be a little bit generous.

Dr. Barry Wilson, Chair

There now appears to be an opportunity, or let's say, an opportunity appears to be arising.

Dr. Claudia Miller

How about efforts should be made to open doors. You may find problems with the State Department in terms of our restricting and embargoing various aid to the country. I don't know if it's going to happen.

Dr. Peter Spencer

It's very carefully written to reflect the fact that the doors are opening on their side. It was meant to imply that the doors are open, that we can walk in those doors, that they appear to be open on that side.

Dr. Barry Wilson, Chair

That's why an alternative is to say, "there appears to be an opportunity." [Simultaneous discussion by panel members continues as to how to word this sentence]. I would not like to be hung up on metaphors. Now, Colonel, do you agree with how he's saying that?

COL Andras Korenyi-Both

If you would be kind enough to repeat the whole sentence?

Dr. Peter Spencer

"The medical doors of Iraq," what was the change?

Dr. Barry Wilson, Chair

"The medical doors of regional allies and of Iraq may now be open." See, that does not imply we are participating at all. Essentially, it's an opportunistic metaphor.

COL Andras Korenyi-Both

I stand away from it.

Dr. Barry Wilson, Chair

You still do not, you wouldn't accept this under any form?

COL Andras Korenyi-Both

My personal experience with this Sir, is that I was invited to this meeting, but at that point, when Iraq learned that I am a full Colonel of the United States Army . . .

Dr. Barry Wilson, Chair

I understand. That's why the word, "may". In other words, we're showing . . .

COL Andras Korenyi-Both

You know, in a free country, we did not used to have this kind of tailored statement.

Dr. Barry Wilson, Chair

I understand. This is not a phrase that's devised in naivete. It's one that's devised on the idea that the health of one, is the health of all, at this stage. Otherwise there will not be no peace. And if Iraq doesn't recognize it, let it be us that has put out the hand. That's what I'm saying.

Dr. Peter Spencer

There's supposed to be an insertion here of "medical door of allies and of Iraq." "Regional allies," sorry.

Dr. Hermona Soreq

Regional.

Dr. Peter Spencer

"Now appear to be opening to international non-governmental medical scientists."

Dr. Barry Wilson, Chair

That is one compromise. The other cop out, well this meets the problem the Colonel had. The other problem is to say that "the medical doors of other countries involved in the conflict," and just drop the word Iraq.

Dr. Claudia Miller

I don't want to delete Iraq. I think we should make overtures to scientists in Iraq and other countries.

Dr. Hermona Soreq

But Claudia, you have high incidence among Iraqi veterans, so…

Dr. Claudia Miller

That's right.

Dr. Barry Wilson, Chair

I didn't say to take it out of the other sentence. I said, "the medical doors of other countries, appear to be opening to international medical scientists," and then you leave Iraq in that credible ending point. It's just that first statement.

COL Andras Korenyi-Both

Sir, why do we need "regional?" That ultimately excludes other members of the coalition forces.

Dr. Barry Wilson, Chair

Countries involved in the conflict, was my suggestion. [The group reaches consensus] Ok we now have consensus - "The medical doors of countries involved in the Gulf War conflict, now appear to be opening." That's the umbrella . . .

Dr. Deborah Norris

Do you want to say all countries?

Dr. Barry Wilson, Chair

No, I'm never going to say all. I always used to cross those out on multiple choice exams. Okay? So Iraq is in there in the statement of the truth. The phenomenon are there. We just don't want to step in something and we can't get our feet out, and it has to be everybody here. Okay, there is one other addition here in the next paragraph. The last sentence is a correction, that's all. Research on *their* mechanisms of action, should be, research on *the* mechanisms of action. And the short-term and long-term adverse health *effects*, so there are two changes there.

Dr. Hermona Soreq

There seems to be one word missing in the opening of this paragraph. To find, to explore.

Dr. Barry Wilson, Chair

We're almost at the point of massaging. This is not a statement for all time. It's just that it does say that we're aware of the broader picture of this and of the way we want to deal with it, and I really do want to thank Dr. Spencer for making this first draft. It's a powerful document. Are we done with it?

Dr. Claudia Miller

I'd like to look at it. One of the concerns I had in the first reading of this, and maybe you can point out where that section is, is this focus we had, which is very strong, about looking at mechanisms that might explain, that would be unifying, and if you could point out to me where that is in the document, it would be very helpful.

Dr. Barry Wilson, Chair

Well, that's going to show up in the objectives statement. That's the next part of this.

Dr. Claudia Miller

We're constituted as a mechanisms/etiologic committee, and the fact that you have Drs. Abou-Donia and Soreq here, we're looking at what I would conceive as a potentially unifying mechanism. Dr. Bell and Dr. Sorg, myself, we're all people that have talked about certain mechanisms, and because those have not been adequately explored in certain cases, is why we're

here.

Dr. Barry Wilson, Chair

Okay, I think we're asking too much of this, Doctor. This is not the entire thing that's to be presented. The next part of it is what we had gone over, which should have the suggestions made yesterday, in it, and I'm trying to find them right now. Where is the other part of the presentation that has the objectives of the research? It's at the end. Dr. Miller is absolutely right. What we need here is a statement of our objectives, which are, to seek unifying mechanisms to understand Gulf War illness. It's that simple.

Then, the objectives are to identify the events or environmental agents precipitating Gulf War illness, to identify the mechanisms leading from exposure to illness, to identify the biochemical and physiological basis of Gulf War symptoms, to develop the scientific basis for the development of treatment and strategies for Gulf War illnesses, and this is to be done with inter-disciplinary research. Now, this is not phrased right. All it is is a bullet and it should come before, but at the moment . . .

Dr. Claudia Miller

Well, my concern is that the preamble is a very nice statement, and our charge is looking at mechanistic hypotheses that have otherwise not been explored adequately, that are unifying.

Dr. Barry Wilson, Chair

This started out yesterday, as just a preamble to give the big picture. Now we move forward, and the other, well, we have two problems. The one was what Dr. Suk was putting together, and the other was the objectives statement, and that's not yet cleaned up, but I can almost dictate that, which is the next part after the preamble, and it's going to be bullets, not this statement, which is in writing. All we're required to do is submit bullets of the committee's work, and this next part is the committee's work.

Dr. Claudia Miller

There is something on the next page, which is seven or eight lines down, where Peter or whoever did this, put in, research should be focused on unifying mechanisms that explain etiology, pathogenesis. I don't know how you explain unifying mechanism for treatment, but anyway, just to place more emphasis on that sentence by highlighting that the committee feels strongly that research should be focused on unifying mechanisms that have the potential to explain.

Dr. Peter Spencer

The reason I didn't emphasize it, is because I don't know what it means.

Dr. Claudia Miller

We've got problems if we don't know what it means. It means that there are mechanisms that have been subscribed, for example, cholinergic super-sensitivity, that's one example. The idea of neurological sensitization, neurolimbic sensitization, toxicant induced loss of tolerance, which at the risk of sandbagging, I'll mention. But there are very specific unifying hypotheses, which is the reason a lot of this committee has been constituted in the manner that it has, and that veterans and their representatives have felt have not been adequately explored by existing research. So, that's really the reason we're here.

Dr. Barry Wilson, Chair

Why don't we say that?

Dr. Peter Spencer

How can you have unifying mechanisms, if you also say there may be multiple forms of disease among this group of people that we refer to as Gulf War unexplained illnesses?

Dr. Claudia Miller

Well, that's the point. These are mechanisms that offer the potential to explain that. The cholinergic system, well, why am I telling you? They're body-wide.

Dr. Barry Wilson, Chair

Hey guys, it's five till nine. Let's get away from who shaves the barber.

Dr. Claudia Miller

This is an important point.

Dr. Barry Wilson, Chair

Why don't we say here that one of the objectives of the committee is to seek unifying mechanisms to understand the etiology or etiologies, if you want to put it in plural, that each one, if there were five different Gulf War illnesses, we'd face five unifying mechanisms we need to be finding out?

Dr. Peter Spencer

Why is the word unifying needed? Why not just mechanisms?

Dr. Barry Wilson, Chair

Call them multi-disciplinary, if you like.

COL Andras Korenyi-Both

She is absolutely right. I'd like to go with her recommendation.

Dr. Barry Wilson, Chair

What was it?

Dr. Claudia Miller

That the committee wishes to emphasize research focused on unifying mechanisms that have the potential to explain multi-system illnesses of Gulf War veterans.

Dr. Barry Wilson

One way to do it, is to violate Dr. Spencer's draft here, and make that a new paragraph, but then you run into a problem, because it really is the end of that paragraph, and the point "to ensure and enhance," should be an end paragraph. And I have skirted and will skirt now, the argument about whether we face whether we have one or more illnesses. If we knew that, we wouldn't have to be meeting.

COL Andras Korenyi-Both

That's correct, but the manifestation is what we are dealing with. The unifying mechanisms . . .

Dr. Barry Wilson, Chair

The unifying mechanisms are what we don't know. That's why I wanted to keep that open. So, what are we saying, then?

Dr. Claudia Miller

I would move that we make a paragraph at the end of "bedside," and take that sentence and put it at the beginning of that paragraph, because that really is the emphasis. Then, the rest of it sort of flows in, about "it should be interactive" and so on and so on; that's all good. But we wish to

emphasize that the research should focus on unifying mechanisms.

Dr. Iris Bell

We've just been discussing this, and in the spirit of what one usually does in an NIH grant, where you in your specific aims right up front, just hit where you're going, I would propose that you name our objectives when you start speaking, before you say any other preamble, literally, so that we get it on the table about where we're going.

Dr. Barry Wilson, Chair

Okay. The objectives that we were talking about then, would come in front of this, and then we would go on to the statement. That's fine, because we are a working group and we are up front with that. So, are we now agreed with this, so we can now move on?

Dr. Claudia Miller

No. It doesn't say what we said. Okay, now we're getting there - "have the potential to explain the multi-system illnesses of the Gulf War veterans." The treatment thing I would leave out.

Dr. Barry Wilson, Chair

This beginning to read like it was written by a committee.

Dr. Claudia Miller

But it is inclusive . . . ".multi-system *symptoms* of the Gulf War veterans."

Dr. Barry Wilson, Chair

Now, to the top of it. We're going to start out with the objectives and that's what I'm going to present, one way or the other, and those are bullets. This is not 'when in the course of human events statements,' this is a . . . yes?

Audience Member

Our concern over there is the phrase that keeps popping up, low-level and non-lethal.

Dr. Barry Wilson, Chair

This is part of the charge of the committee into what we were given.

Audience Member

Okay, because on the burial detail at the Legion, we're burying guys weekly, and my buddies and my unit is diminished to nothing, so non-lethal doesn't apply..

Dr. Barry Wilson, Chair

Okay. What that means, there is a word that should be in there. I don't know if we've got the time now, the word is acute, okay? That's what we're faced with in this.

Audience Member

And that wouldn't be in there, why?

Dr. Barry Wilson, Chair

No, it just got dropped out. The word acute is what is meant in there.

Dr. Sheila Newton

Right. It just meant the exposures were not lethal immediately.

Dr. Barry Wilson, Chair

And we should slip in that word, acute, and that answers your objection, Sir.

Audience Member

How can you say that? There's direct evidence of that with the animals and personnel, there was, pardon my French, but, dead ass everywhere.

Dr. Barry Wilson, Chair

At the time of the Gulf War?

Audience Member

Yes.

Audience Member

Absolutely.

Dr. Barry Wilson, Chair

There were, how many people died?

Audience Member

U.S. casualties, or overall?

Dr. Barry Wilson, Chair

No, I'm talking about how many people died from unexplained illnesses?

Audience Member

Thousands, in Iraq. If you want to talk, I was talking about animals that were in direct relation to chemicals, because they didn't have bullet holes in them.

Dr. Barry Wilson, Chair

You have put me into something that I cannot handle. Seriously. This was one of our charges. I mean, you can't open at the last minute to us…

Audience Member

Can't you just put low-level, non-lethal and lethal? Just add that one word to it?

Dr. Barry Wilson, Chair

Okay, fine by me. I'm not, hey man, I'm not a cover-up. I've got no blanket that I can even suck on.

Audience Member

I appreciate it. Thank you.

Dr. Iris Bell

I was going to propose when we get to prioritizing the research proposals that we actually take a look at prioritizing degenerative disorders that could be lethal as a first, top priority, so I think we

should consider that that would be a place to emphasize it.

Dr. Barry Wilson, Chair

We were told to focus on the low-level. Let it go right now, we can clean it up later. We're out of time. We move on. Okay? Now, the objectives at the beginning, and then we move to the bullets, because if we don't get the priorities, we go anyway.

Dr. Claudia Miller

The primary objective is really at the end of this, so we should move this to the top.

Dr. Barry Wilson, Chair

I wanted to take the objectives, way at the bottom of the bullets and move that up front. She's got some troubles getting these together, but it was a very good idea to start out with the bullets that are on the other document. And now, those were the objectives as they were synthesized quite well by someone from the audience yesterday, and we are incorporating them. Now, we have to incorporate them quickly and without a lot of quibbling.

Dr. Hermona Soreq

In the fourth objective, I would think that we need to say "to establish." In the fourth objective "development" seems to be redundant, so I would suggest "to establish the development".

Dr. Barry Wilson, Chair

Let's take a look at what we've got. It's very hard to write in public. The objectives, and it could just stay as bullets, that's fine with me. What Dr. Miller is saying is that number 4, now comes up - "the major objective is to identify the events or environmental agents precipitating Gulf War illnesses and to identify the biochemical . . ." I'd put 3 next. "The biochemical and physiological bases of Gulf War Veterans' illnesses." The word symptom always bothers me. Then third, is "to identify the mechanisms that lead from exposure to symptoms." That goes from the molecular all the way up through the physiological into the human level.

Audience Member

Does that support page 32?

Dr. Barry Wilson, Chair

It better. This is science. This is the right way. I'm not even going to look, because with these Objectives, we're standing on our science now. What we're saying is to:

- Identify the events or agents that precipitated the Gulf War Illnesses
- Identify the biochemical and physiological basis
- Identify the mechanisms that lead from exposure to symptoms
- Establish a scientific bases for the treatments of Gulf War Illnesses

That's the way I would read it, no matter how it's written. Find out what did it, how it did it, and how you fix it. It's that simple. That's what goes behind the science, and that's our business. This is what we felt are charge to be, here is a general statement that is written and carefully considered, then third, we move to look at the list. I would ask us first to think about this list . . .

Dr. Deborah Norris

Before we move on to the third phase, Mr. Chair, I have lingering concern about the preamble that I would like to address. The last sentence where we say we are only interested in low-level and sub-lethal exposures. I have heard of many instances where the soldiers were exposed not to low level or sub-lethal, and I would hate to imply that we are not interested.

Dr. Iris Bell

I'd rather not lose the low-level concept, but we could make a list of hierarchy, low-level, sub-lethal and lethal.

Dr. Barry Wilson, Chair

Let's just say of acute, low-level and sub-lethal exposures. If people feel there was acute exposure, then let's put the word acute in, and that's very satisfying to any toxicologist. That's the way we think about it - acute, low- level, and sub-lethal. I would have inserted the word chronic..

COL Andras Korenyi-Both

Then, sub-acute and chronic.

Panel Member

That would be in place of short . . .

Dr. Deborah Norris

Are you talking about acute effects or acute exposure?

Dr. Barry Wilson, Chair

Short and long term adverse health effects of acute, low-level, and sub-lethal exposures, you can have short- and long-term effects of an acute exposure. I was afraid to use the word chronic, because it didn't run that long. Can we just go with this part? It has the word acute in it.

Dr. David Ashley

My question about the sentence is it's saying someone else set these up as national priorities. This has nothing to do with what we're saying today. Which is it? What are the national priorities that have been set?

Dr. Barry Wilson, Chair

Why don't we just forget the national priorities and say that "we recommend research on . . ."

Dr. Sheila Newton

I think what he's trying to say is that part of the reason that we are meeting here in the first place is that people have recognized the importance of these exposures. So we don't have to say national priorities, if we think that implies some sort of formalization, which it doesn't, I mean, which it isn't intended to, but you can say, it has been recognized that . . .

Dr. Deborah Norris

But are we going to ignore any high level exposures?

Dr. Barry Wilson, Chair

No, we have the word acute in there now. It's not being ignored. To quibble over the words in this, by tomorrow, all of us would want to re-write it when we sat down and looked at it. I think Dr. Spencer gave us a draft that's a magnificent job. Instead of relying on my rhetoric, we can rely on his paragraphs. Do you want to leave in the national priorities or not? We've got to move on.

Dr. Claudia Miller

I have some additional language that Peter and I are hammering out here.

Dr. Barry Wilson, Chair

Then we will not get to the other priorities or anything, okay? We are out of time.

Dr. Iris Bell

Can we come back to them, if we can? I think it's very important to discuss the priorities.

Dr. Barry Wilson, Chair

Yes, so do I. We can just sort of go with this now, and tell them this is a draft, if you'd like.

Dr. Claudia Miller

Can I read it? And if everyone likes it, we'll add it. We'll stop. Peter suggested we add - "There are also veterans with severe medical disorders of unknown cause. These illnesses should be individually studied for their possible etiological relationship with exposures in the theater of war. In addition, veterans with acute onset of illness following a well-identified exposure event such as vaccinations or pesticides exposure, should be studied to learn about possible etiologies."
Dr. Barry Wilson, Chair

I think it will be redundant when we show the list we have.

Dr. Hermona Soreq

I think the essence is already in there. I think if we write too long a statement, no one will listen.

Dr. Iris Bell

I would rather that we develop a short list of bullets of what our priorities are to put at the top of our list of specific things that we developed yesterday.

Dr. Barry Wilson, Chair

Do you want to go to the bullets now? We have to, or they go as they are. First of all, we have an impossible task here. We want short-term, long-term and then you want to condense the bullets, which will take another day, but let's see what happens.

Dr. Iris Bell

No, I think we should create some new bullets at the top of the document that we created

yesterday, and say here are our priorities in this list.

Dr. Barry Wilson, Chair

Do you have them?

Dr. Iris Bell

Well, I made mine.

Dr. Barry Wilson, Chair

Why don't you give them to us now, and we'll put them up there.

Dr. Iris Bell

In terms of exposures, I was thinking in terms of data gaps. Number one would be depleted uranium, the second would be multiple interactive exposures . . .

Dr. Barry Wilson, Chair

That may not be quite the way to phrase it, but I agree with what you want.

COL Andras Korenyi-Both

Excuse me, Sir. We really are running out of time. We are trying to prioritize. Why don't we put them in alphabetical order. In that case, let somebody else prioritize, or we'll be here the next 24 hours.

Dr. Barry Wilson, Chair

Thank you, I agree. I know we will not make it, but let's have these few bullets of our emphasis.

COL Andras Korenyi-Both

Let me say that depleted uranium is in the front line and research is ongoing is very important. I feel that alphabetical order would save us.

Dr. Barry Wilson, Chair

I think we don't need to change the whole thing, but I think what we are seeing now is the end of

the level of where we are all agreed to things and it would take us quite a time to do it. I know Dr. Bell has worked and thought long and hard on that list. I know I worked and thought hard about mine. Maybe we just can't get there from here, given the way this was all structured and put together. The Colonel is right, but I don't like the alphabetizing. I will just go with what I've got.

Dr. Iris Bell

There are certain issues that emerged during this meeting. One of them being uranium, from the veterans, and certainly one them being the multiple interactive exposures, and the bullets highlight that because otherwise we have a laundry list of individual agents which people might chose to study individually.

Dr. Barry Wilson, Chair

Would you guys trust me that I will emphasize that when I present our short report.

Dr. Claudia Miller

Dr. Somani and I just compared our highlighted bullets and they were completely different, so we are going to have trouble getting agreement.

Dr. Barry Wilson, Chair

That is what I am afraid of. I am trying to pull us together and I would not like us to walk out of this room feeling badly.

Dr. Iris Bell

The other prioritization, again, I had around conditions and there were three of them that I want to propose. The first would be degenerative conditions such as cancer and neuro-degenerative disorders that have claimed to be emerging among the veterans. The second is complex cognitive problems, because the data in other more standard research, indicates that those have the largest impact on an individual's ability to function in society. The third is multi-system conditions, especially problems such as chemical sensitivity, chronic fatigue syndrome, and so on. I'm saying highlighting from our long list.

Dr. Deborah Norris

I strongly disagree with comparing health effects and saying one ranks more important than another.

Dr. Barry Wilson, Chair

All you have to do is say "No." I afraid we can't get there from here, I think that we've gotten as far as we can go.

Dr. Peter Spencer

Could someone speak to the justification of including lead in that list?

Dr. Claudia Miller

Leaded fuels were a concern for some veterans, used in tent heaters and vehicles and such.

Dr. Barry Wilson, Chair

That doesn't mean it might not end up being excluded after the work.

Dr. Claudia Miller

Their testing has been negative. That's right, so I wouldn't put it on my list.

Dr. Hermona Soreq

I wanted to suggest two minor changes on the list of bullets. For one thing, porphyria . Porphyria was mentioned yesterday, but I don't know of any evidence that relates it. And we were asked to limit the list to issues that are of major concern. I don't see that this is a major concern. If we say, "e.g., cholinesterase," that includes anything else that might be found, but one mentions something that is notably non-relevant. So my suggestion is to drop that.

Dr. Iris Bell

I don't have a problem with doing that. The porphyrias are one of the proposed mechanisms for chemical sensitivities, though they would be subsumed under chemical sensitivity.

Dr. Barry Wilson, Chair

Well, if it's subsumed, we can just say, we want to study chemical sensitivity.

COL Andras Korenyi-Both

Stay as it is.

Dr. Barry Wilson, Chair

Stay as it is.

Dr. Hermona Soreq

Number two is, I've re-read the pages of our charges and we were not asked to comment on medical treatment. We were asked to comment on research. So my suggestion is in the last item under special needs, to change the word "medical unit," which may create problems, I think, into "research facilities for special technologies." That would be under our mandate, I think, otherwise I afraid this may be dropped off.

Dr. Iris Bell

Can we change the word "medical unit" to "research unit?"

Dr. Claudia Miller

Well, there's a very specific thing here, what you're dealing with. That has been the inability of agencies to fund environmentally controlled hospital facilities to adequately evaluate low-level exposure effects, so I would opt that we leave this in as it is. If we want to add an additional statement that other research equipment, that would be fine.

Dr. Barry Wilson, Chair

There may be a split on the committee here.

COL Andras Korenyi-Both

I believe that medical unit is a more target-oriented expression.

Dr. Iris Bell

We're not proposing a specific clinical treatment program right now, we're proposing research in that area.

Dr. Barry Wilson, Chair

How do you want to phrase this? Because if you hold to this, I'm not pleased about this at all. Okay, let's settle this, it's twenty-five after.

Dr. Hermona Soreq

I was thinking, "research facilities for special technologies" which is in our charge and would probably not raise problems.

Dr. Claudia Miller

How about research facilities for special applications, e.g.; for example, special applications.

Dr. Barry Wilson, Chair

Your suggestion again, Dr. Soreq.

Dr. Hermona Soreq

Research facilities for special applications.

Dr. Barry Wilson, Chair

Okay. Are we agreed? No?

Dr. Claudia Miller

You're talking about a hospital unit. This is different from facility.

Dr. Barry Wilson, Chair

Look, I'll drop the whole thing out. I'm saying as the Chair, you may have nothing right now. I may drop it out. I'm going to take a vote now. [Committee voted for "controlled environment medical research unit.] Okay. Moving on to the audience now.

Mr. Richard Wadzinski

I'd just like to make a closing remark to this, before this all becomes etched in stone. What items in this research program are going to help sick vets get a better understanding of their illnesses? It's essential that any research program, leaving this meeting, as a recommendation, will produce a basis for hope in sick vets to include the etiology, assessments, diagnoses, and far more important, treatment, and create prevention for future vets. And I add onto that, there are still folks over there. Another point, what's going to be done for vets like myself and others with organ transplants, failing organs and we are receiving rejection medication, steroids, how do we fit into the research and treatment? And last, don't get too offended, Sir, you can't say the war is

over, because they are still there, they're still fighting. The only person that can say the war is over is the Commander in Chief, the President, and until all the vets are pulled out and come home, then the war is over.

Dr. Barry Wilson, Chair

Will you forgive my big mouth? I am sorry. I apologize. What you said now, I wish you'd say to the plenary Session, and I wish you'd stand there with me when I start out. Except, dropping the part about chewing me out for saying the war is over. It's not written anywhere and I've just taken it back, and I've got to go wash my face. So . . .

C. Kirt Love
Signing My Life Away
Copperas Cove, Texas

I would like to keep the lead in for the simple reason that, when we were there, we had to go into the local communities and buy equipment that we needed. We had to buy things that did not fall under American standards of product quality, we dealt with a lot of odds and ends and things that we kept in the tents with us that were very questionable. We had to do what we had to do. We had to work with everything we had. We're not sure. There's still, even some of the ammunition was lead based. If it's been atomized and mixed with the sand and blown with the sand storms, it might be part of it, lead being a poison.

The second thing I'd like to address is, I deal with veterans from Desert Strike and Desert Thunder who are sick, who don't know and don't understand what's happened to them because this isn't Desert Storm for them. They didn't participate in that, but it's the same region, the same problems. I'm seeing this with EOD, the people who are still blowing bunkers and still blowing munitions in the area, because they find it scattered everywhere. So I really hope that we encompass just a little more than just Desert Storm because this is still an ongoing process for us.

Dr. Barry Wilson, Chair

I didn't think that we were excluding it. And secondly, you want lead in? Lead's in. It may not survive the research, but it's in.

Mr. Kirt Love

Thank you, Sir. I just wanted to, instead of waiting to get to the next room to fight the process.

Dr. Barry Wilson, Chair

It's in and our time is about up.

Audience Member

Can we change heavy lead to heavy metals? There may be more than one. There are other heavy metals, like cadmium.

Dr. Barry Wilson, Chair

Will you accept heavy metals? Toxicologically, I'd have to absolutely agree. [Agreement expressed among panel members].

Dr. Barry Wilson, Chair

We have done the best. It's neither Shakespeare nor Sartre, but it's not the morning news. Thank you all very, very much.

The session was adjourned.

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